Obesity & Cancer Webinar Series

Intersectionality of Obesity, Cancer, and Basic/Translational Health Disparities Research Webinar
March 11, 2021, 3:00-4:30 p.m. (Eastern Time)

Webinar Questions and Answers

Moderator:

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Panelists:

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1. **Within strata of age at diagnosis and disease status, is BMI a predictor of survival?**

   Lucio Miele, M.D., Ph.D.: In our analysis, that didn't seem to be the case. But there may not have been enough statistical power, because once you start breaking down even a large dataset into multiple categories, you start losing statistical power. That's a very worthwhile question, and I think we should investigate it, particularly in younger patients. Because, as I said earlier, screening is not going to correct that disparity. These are people who are in their 30s, and in some cases that I personally witnessed, even younger. They are not going to be eligible for mammography, so we need to know whether in that age group there are predisposing factors tied to body mass that can tell us to start screening much earlier or do something different.

2. **There is significant individual variability in insulin resistance—what about Asians?**

   Victoria Seewaldt, M.D.: Yes, this is really important. In Los Angeles, we have people who are sixth- and even seventh-generation American who came originally from Asia, China in particular. As these individuals have adopted Western diets, their BMIs have increased proportionally. It's really easy to get fooled because you may see a woman in clinic who is Asian and has a BMI of 22 or 23. With a Northern European-centric view of medicine, you may say that a BMI of 22 or 23 is perfect. Actually, these individuals have a very high likelihood, particularly if they're in their 50s and 60s of being pre-diabetic or having type-2 diabetes. So, it's very important to think carefully about the person and not just apply cookie-cutter, one-size-fits-all Northern European-centric medicine to the diverse individuals who live in the United State. Many women, not just Asians, are at increased risk for type-2 diabetes and pre-diabetes. Those from India, the Middle East, and the Philippines are at risk at a BMI that for Northern Europeans would be considered low risk. Unfortunately, most of the world's insulin sensitivity and metabolic dysfunction is not captured by a Northern European-centric viewpoint.

3. **Is bariatric surgery the only hope for obese people who are having trouble losing weight?**

   Augusto Ochoa, M.D.: No, bariatric surgery is one of many approaches to addressing extreme obesity and metabolic syndrome, but it is clearly not the only approach. Work done with other approaches including diet and exercise have also shown some benefit. For example, a study comparing the effect on weight loss on inflammation in adolescent girls with asthma through diet and exercise showed an improvement in inflammatory markers in those individuals who achieved significant weight loss and control of metabolic syndrome. I also understand that Dr. Seewaldt has been doing some similar work with patients with breast cancer.

   Victoria Seewaldt, M.D.: I don't think we have the data that Dr. Ochoa would like us to have. We have been partnering with women who start metformin and test whether we're able to reverse their prediabetes and insulin resistance. In our ongoing ALLIANCE trial testing metformin vs. placebo in women with precancerous breast changes (cytologic atypia), we will be testing whether metformin decreases inflammatory score in the breast aspirates. We haven't finished collecting all our data, so I can't comment at this point, but I'm hoping that we can get this data soon for Dr. Ochoa.

4. **Is epigenetics primarily related to socioeconomics?**

   Victoria Seewaldt, M.D.: I'm going to talk about epigenetics, and then I think I'm going to need some help from my friends. People who live in underserved neighborhoods lack access to healthy foods; are exposed to carcinogens in the air, water, and soil; and are likely to develop type-2 diabetes. The first step in developing diabetes is insulin-resistances (high

insulin and ultimately high glucose). One thing that is known about high insulin and glucose is that insulin/glucose overdrives the mitochondria, and there is excess production of acetyl-co-A. Unless it is being transcribed, DNA is normally wound around histones. DNA (which is negatively charged) is attracted to lysine residues on the histone (which are positively charges). However, if there is high production of acetyl co-A, the acetyl-co-A binds to histone lysines and displaces the DNA on the histones. This displacement results in inappropriate transcription.

There are many other epigenetic changes brought on by high insulin and high glucose. In people with type I diabetes, Rama Natarajan from City of Hope found that high insulin and glucose (poor metabolic control) resulted in permanent epigenetic changes that drove damage to large and small blood vessels that could not be reversed ("epigenetic memory"). We strongly suspect that in individuals at risk for type-2 diabetes, early identification and prevention of pre-diabetes can prevent epigenetic damage and damage to the blood vessels. What we don't know is whether early detection and reversal of pre-diabetes/insulin-resistance can reverse pre-existing damage. In any event, damage to the blood vessels starts very early. There is a need for health care for all people, particularly those living in underserved zip codes, to provide consistent early detection and prevention.

Lucio Miele, M.D., Ph.D.: Everybody's familiar with the famous study of Pima Indians in Arizona and Mexico. It was an NIH study, in which investigators that are now at Pennington Biomedical Research Center participated. People hunted for the genes responsible for the dramatic difference in obesity and diabetes between north and south of the border and found nothing. And eventually, it turned out that this is a very genetically homogeneous population. The difference was epigenetic and inheritable. That's the scary part.

Augusto Ochoa, M.D.: There is a relatively new concept in immunology on "trained myeloid cells," which is caused by epigenetic changes. These trained myeloid cells then develop an increased or a suppressed response to secondary signals coming from cancer or infectious agents. There is also an increasing body of literature showing how dietary elements may modify these trained myeloid cells. However, I believe we are still using very blunt instruments to understand what's happening. We will need to use finer tools to understand the biological implication of these epigenetic changes. An example is a recent publication by Marcia Haigis's group from Harvard showing epigenetic changes in T cells in an obese tumor microenvironment in mice. I believe this is the type of information that will help us better understand the effect of obesity on inflammation.

5. If BMI is not the predictor, what aspect of obesity and/or inflammation could be a predictive marker?

Lucio Miele, M.D., Ph.D.: In my opinion, we need to look at laboratory parameters. There is something called the Edmonton obesity staging scale, which includes a lot of other data

elements, some of which can be derived from the EHR. We actually have written code to calculate an EOSS (Edmonton Obesity Staging System) score from the EHR. It's a lot more laborious than simply measuring people, but it tells you whether somebody has elevated hemoglobin HgbA1c and whether somebody's hyperinsulinemic as defined by the diagnosis of prediabetes. You can pull out the labs that let you determine whether somebody has metabolic syndrome. We've got to look at the clinical chemistry as amenable, in addition to just body mass.

Victoria Seewaldt, M.D.: I agree with Dr. Miele very strongly here. I think we need more studies. And I think that we need studies that consider the whole person. As all of our speakers have alluded to, this type of study is more difficult, but really understanding individuals rather than one-size-fits all generalizations is going to be key to really starting to look at what predicts, like Dr. Ochoa said, tissue inflammation. Just looking at BMI alone is really not giving us the entire picture.

6. **Along these lines of BMI, should the field be moving towards using DEXA scans (bone density scan) as a more accurate predictor of a person's health/adiposity (fat:muscle:bone ratios)? Maybe this measurement will allow researchers to increase the resolution of our experimental approaches?**

Victoria Seewaldt, M.D.: I've got to hearken back to all of our breast cancer trials. While I think people haven't specifically used DEXA scans, they've used waist-hip measurements. And even using waist-hip measurements, the results have been complex. I agree that it's very reasonable to look in more detail at the distribution of the fat and look, as I think Dr. Ochoa said, with finer tweezers. However, I think we also have to look at metabolic health and biomarkers, particularly tissue-based biomarkers.

7. **Could HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) be used instead of BMI? Some populations are more insulin-resistant by HOMA-IR for the same BMI.**

Victoria Seewaldt, M.D.: Yes, and we're using that currently in our ALLIANCE trial, but I think, as the other panelists have alluded to, we're only scratching the surface. As illustrated by Dr. Ochoa's example of people with, 1) inflamed fat vs. 2) people who have high BMIs and no inflammation, we still need to think deeper than we're doing. I'd like to make a pitch here for the importance of improved healthcare. In Louisiana with the adoption of the Affordable Care Act, they've really made an impact on the health of their state. But what happens is that, for a lot of women, there's fragmented healthcare. For example, a woman goes in for her pregnancy care. She may gain some weight, she may have gestational diabetes, but like many women, when her pregnancy ends, she doesn't have the healthcare coverage to go and deal with the prediabetes or insulin resistance that might have occurred. If a woman then has a second pregnancy, it is likely that her pre-diabetes and insulin-resistance will be worse. This argues for early and consistent healthcare because the

Diabetes Prevention Program (DPP) shows that over 45% of diabetes can be prevented with the use of just gentle exercise, a reasonable diet, and the addition of metformin. The DPP is one of the most impactful trials conducted in the United States. But even though the findings have been translated to American Diabetes Clinical Guidelines, many primary care physicians do not follow them – as physicians we just sit there, follow people clinically, measure their weight and HgbA1c, and wait until people become diabetic. Then we finally say, oh, gee, let's give them metformin and ultimately, insulin.

Augusto Ochoa, M.D.: I think the other aspect of this is that while models of obesity in mice may give us some clues and tools to work with, nothing can replace the information that we can glean from patient studies. Both obese patients with and without cancer will be needed for better understanding of the mechanisms that increase the risk for cancer in obesity.

Lucio Miele, M.D., Ph.D.: And when patients present to oncologists with dysmetabolism or diabetes or obesity, we don't do much about it. Maybe we'll refer them to an endocrinologist or maybe not. Some of us are terrified of even talking about issues of weight with patients because it's a little sensitive. As you said, we don't want to give the impression that this is a matter of willpower or blaming patients for gaining weight. But we do have to emphasize that gaining weight is not healthy, that it's biology, and it can and should be corrected. That should become part of oncology.

8. **Could the panel discuss potential roles and involvement of high fructose corn syrup that is an indispensable component of Western diets? The metabolic changes/alterations could be influenced by this prevalent dietary constituent that could contribute to diet-induced obesity, particularly in low socioeconomic populations.**

Victoria Seewaldt, M.D.: I think that high fructose corn syrup has caused major damage to the health of people in the United States and internationally. To illustrate this, we have a community-based intervention trial that uses education and a little bit of group exercise to prevent type-2 diabetes. The program is primarily focused on Latinas and it's run by our Latina *promotoras*. The program teaches people to shop on the outside aisles of the supermarket. The inside aisles of grocery stores house all the junk food and high-calorie foods containing high fructose corn syrup. The outside lanes are where the healthy food is located – vegetables, proteins, dairy, and minimal processed food. With very simple intervention, just a little bit of community-based exercise and shopping on the outside aisles of the supermarket, women have been able to reverse insulin resistance and prediabetes. So, I think part of it is the stuff on the inside aisles of our supermarkets – with all the processed foods containing high fructose corn syrup that are causing much damage to the health of our people.

9. **How can anti-inflammatory drug strategies reduce the risk of cancer and/or treat cancer?**

   Lucio Miele, M.D., Ph.D.: That's a complicated one, because there are different classes of these drugs, not all of which have the same effects. Some of them have anticancer effects that are off target. They're not actually mediated by COX inhibition. That said, that is a field that should be investigated. The last time I gave a talk about this to our friends at the Mayo Clinic, what I heard was, "That's fantastic, but no one's ever going to want to fund this kind of study because there are no new medications to be developed here." Prostaglandins E2, which is the main target of many NSAIDs is one of the most potent immunosuppressants. It blocks the T-cell activation. So, there is a mechanistic reason for taking that. We just have to go into deeper detail, as Dr. Ochoa was saying earlier, deciding which class of drug and which member of which class of drug works better. But repurposing is the key.

   Augusto Ochoa, M.D.: We already have thousands of drugs that are approved for other indications that also have an impact on immunity overall. For example, one of our investigators, Dr. Yaguang Xi, while looking at an old anti-inflammatory, sulindac, has found that it has a major impact in the expression of PDL1 and the function of MDSC (Myeloid-derived suppressor cells). I believe we can repurpose many drugs by further understanding their impact on inflammation, even if they do not have an impact on obesity or metabolic syndrome.

10. **Is there a difference in MDSC patterns for microsatellite unstable vs microsatellite stable colon cancers?**

    Augusto Ochoa, M.D.: We have not specifically studied MDSC in patients with or without microsatellite instability-associated colon cancer. I believe, however, that this would be a very interesting question for study.

11. **I want to especially understand whether I heard correctly that propensity for development of type-2 diabetes can become imprinted epigenetically and therefore inherited?**

    Victoria Seewaldt, M.D.: I apologize if I misspoke. Imprinting is complex (see reviews by Randy Jirtle for more information). Genes for energy utilization and growth have a paternal origin of imprinting. This means that if your father had a poor diet, it is possible to pass on these imprint marks. I think that there needs to be greater study of imprinting before it is possible to say that abnormal paternal imprinting of growth regulatory and/or metabolic genes causes type-2 diabetes.

12. Is there a correlation between BMI and liver cirrhosis/liver cancer?

Victoria Seewaldt, M.D.: Yes, definitely. There is currently an epidemic of obesity-linked fatty liver, liver fibrosis, and liver cancer. It is also suspected that environmental carcinogens such as arsenic may also worsen this.

13. Are there any known SNP (single nucleotide polymorphisms) that make Asians more susceptible to metabolic syndrome caused by a Western diet?

Lucio Miele, M.D., Ph.D.: There a number of GWAs (genome-wide association studies) identifying potential SNPs associated with dysmetabolism in various Asian populations. For example: Genome-wide association study of metabolic syndrome in Korean populations; Association of BDNF rs6265 and MC4R rs17782313 with metabolic syndrome in Pakistanis; Susceptibility loci for metabolic syndrome and metabolic components identified in Han Chinese: a multi-stage genome-wide association study. These would have to be replicated in larger samples.

14. How exactly does obesity raise the risk for inflammation and cancer formation?

Augusto Ochoa, M.D.: Obesity increases the production of pro-inflammatory cytokines (IL-6) and colony-stimulating factors such as G and GM-CSF from adipocytes, which in turn stimulate the production of inflammatory cells such as MDSC from the bone marrow. Furthermore, it increases the infiltration of adipose tissue by inflammatory cells.

Lucio Miele, M.D., Ph.D.: There are several theories. Adipose tissue produces a variety of soluble factors including VEGF (vascular endothelial growth factor), TGF-beta (transforming growth factor beta) and others that affect the bone marrow and immune cells. VEGF stimulates the production of MDSC, which promote chronic inflammation and suppress adaptive immunity. Adipokines like leptin crosstalk with cancer cells.

15. Can anti-inflammatory strategies reduce either the risk of cancer or treat cancer?

Victoria Seewaldt, M.D.: Yes – potentially. Aspirin is anti-inflammatory and epidemiological studies show a link between aspirin use and reduced cancer risk. However, there need to be prospective prevention studies, as the epidemiologic results are not always consistent.

Augusto Ochoa, M.D.: Yes, extensive clinical trials have shown that in certain conditions that predispose to cancer, such as familial polyposis of the colon, the use of anti-inflammatories can decrease the incidence of cancer in these patients.

16. If BMI is not a good marker, what other biomarkers do you suggest? IGF (insulin-like growth factor) pathway markers? A composite/panel of biomarkers? The other issue with blood markers has been the need for fasting blood, which renders many cohorts of limited value to study the obesity-cancer link.

Victoria Seewaldt, M.D.: I agree that insulin, glucose, and serum lipids are impacted by what individuals eat. We have used HgbA1c because it measures a three-month measure (life of the red blood cell) of average serum glucose. HgbA1c is frequently measured by primary care doctors, and it is usually available on retrospective trials. For interventional trials, if we suspect that someone is insulin resistant but their HgbA1c is normal, we consider further testing of glucose tolerance.