# Obesity & Cancer Webinar Series:
# The Challenges with Cancer, Obesity and COVID-19
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## Webinar Questions and Answers

## Panelists:

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1. **What do we know about obesity and long-term COVID-19 effects, the so-called "long hauler" syndrome? Are there plans to look at some of these longer-term effects and associations with obesity?**

   **Barry Popkin:** I really can't answer that at this point. We really don't have those kind of studies and data yet. I'm sure there are effects particularly because of the lung function issues, but I can't say more.

   **Jeremy Warner:** When we talk about the COVID-19 & Cancer Consortium, I like to say it's really true that we've been "building the airplane in the air". When we began, we didn't really think beyond 30 days of follow-up. Clearly, that's not enough. Fortunately, even though the mortality is high, there are many survivors. So, we now collect 90-day and 180-day outcomes. But, will that be enough? I don't know. We'll probably have to go longer than that. I do think that steroids are pretty popular to treat COVID-19 these days, and I don't think that's going to help obesity. It might be short-course, but sometimes it's not so short. Plenty of people get 10 days of high-dose dexamethasone, and then perhaps are on a slow taper if their pulmonary symptoms do not resolve. We've certainly seen that patients with hematologic malignancy can have prolonged viral shedding and prolonged symptoms, and they may end up on steroids for a very long time, which will certainly not help with their body mass composition and these questions of sarcopenia and the like. But I think we are going to have to gather that data and figure it out in a longitudinal manner, whether it be through our consortium, or through other more prospective trials.

2. **Regarding the study presented by Dr. Popkin conducted in Peru, there was an indication that folks had heard that eating a lot of fruits and vegetables would reduce the risk of COVID-19, and this affected their eating habits. Was there any indication about messaging? How did they hear this? Was it rumor? Was this something possibly conveyed by authorities?**

   **Barry Popkin:** There was no messaging. In fact, we've done these surveys in six countries, and we haven't really seen the kind of messaging beyond just dealing with COVID-19 protection about healthy living, healthy eating, trying to be active, et cetera. In the case of Peru, what was unique was that they had a complete lockdown. In fact, the military patrolled the streets. You couldn't go out. So, it was a serious lockdown. I think it really happened through rumors, through Facebook, websites, and tweeting. In their case, WhatsApp is a very huge, popular communication option. So, that's all we know. It was quite surprising. We followed the media completely in a couple of our countries, and we haven't seen either from the government any discussion beyond dealing with the calamity in terms of their health systems. There's been no focus on encouraging people on what to eat or how to move.

3. **Dr. Warner, did your analysis look at current weight and BMI among patients with cancer, given that cancer patients and especially those with progressive disease have likely already experienced weight loss? Would that perhaps skew your results in some way?**

   **Jeremy Warner:** The practicalities of getting this done or getting these cases reported are such that we do not ask for repeated measures of things, such as weight or laboratory values. So, we essentially collect weight at baseline or at presentation. This is a great opportunity for electronic health records. I'm an electronic health records researcher, and that's most of what I did before I pivoted to COVID-19. Right now, our survey depends on an "army" if you will, of manual entry. We are thinking of ways to pivot to a more automated collection. Certainly, there are others at the N3C effort through NCATS and others that are leveraging the electronic health record environments that most institutions have now. So, we're thinking about that, but we certainly don't want to ask our survey respondents to go back and enter serial weights over a prolonged period of time. That's just a practical tradeoff, but it's a great point.

4. **The racial disparities in COVID-19 outcomes have rightfully received a lot of attention, as you know. From your data and experience, do you have any thoughts about mechanisms or interpretations of these disparities?**

   **Jeremy Warner:** We're in the middle of a new analysis looking specifically at this question, looking at non-Hispanic Blacks versus non-Hispanic Whites. Our hypothesis is that these findings are driven by sociodemographic factors and not anything innately genetic or related to the underlying individuals. I think that there's some very recent data, not on patients with cancer, but more generally, that may support that assertion. We certainly see that non-Hispanic Black patients present with a higher severity of COVID-19 illness and complications. So, by the time they present for care, they have a more severe case. Now, why is that? I can't answer

that right now because we're in the middle of the analysis. It seems to me that it's going to be related to socioeconomic status, access to health care, access to tertiary care– versus not, and so forth. So, I do believe that those are the major drivers that we're going to see.

**Barry Popkin:** We must remember Native Americans first, and then African Americans and Hispanics have very high levels of obesity. BMI levels over 35, 40, 45, much higher than among non-Hispanic whites, so that when we think not only of obesity but extreme obesity, then we begin to see additional risk factors that come into play.

5. **What is it about individuals with obesity that makes the vaccine less effective on them? Do you have any speculation about that?**

   **Barry Popkin:** No. The research on mice and humans with the coronavirus flu vaccine have kind of indicated a lot had to do with T-cell changes and the immune impairment. It also came through the adipose inflammation. It is through these two pathways that come together, and we have to remember that obesity is a cumulative process. These are active cells, as Dr. Nebeling said, "living cells". They are actively producing this inflammation and T-cell responses over time. So, this is an impact, as is the case with cancers and their effects on our system. We don't have a study on just becoming obese. We have studies on individuals with obesity, and most individuals age 40 and beyond have been obese for quite a while.

6. **Have you looked at different levels of obesity and separated those out through morbidly obese?**

   **Barry Popkin:** These were meta-analyses, and they weren't there. We don't have access to a database like Dr. Warner's. If they had a control that went with their database, they could clearly look at all of these issues separately and in various ways with other controls. What I will say is that following along that, we just presented some data at the American Society of Hematology conference on thrombosis in patients with COVID-19 and cancer. It does seem that morbid obesity, or a BMI above 35 or 40, depending how you wish to define that, appears to be associated with increased rate of thrombosis in these patients. The event rates are pretty small. Thromboses are sort of overt as opposed to the microthrombi, which we do think affects most patients with COVID-19. The overt thromboses only occur in 2 or 3 percent. So, it's relatively uncommon. Even so, we still see that morbid obesity appears to modify that risk.

7. **Could this data be used to support prioritization of COVID-19 vaccination for cancer patients?**

   **Jeremy Warner:** Patients with cancer were more or less systematically excluded from the vaccine trials because of their cancer history or other exclusion criteria, such as being immunosuppressed or on some kind of recent therapy, such as chemotherapy. Obviously, we need to know a lot more than we know right now, both about efficacy and safety. We hope to utilize our apparatus that we've built to collect that information. We have a variable that was added after Canada approved the Pfizer vaccine. I treat patients with hematologic malignancy. I'm very concerned about their ability to mount an appropriate response or an immunologic response.

That doesn't mean they shouldn't get the vaccine. There is a question of prioritization, which is inevitable when you don't have enough doses for the total population. Certainly, the people around them should be vaccinated, and this is what we advise for the flu vaccine and all the others, like in patients who've gone through a transplant. We always advise that their local "herd", or everybody who might have contact with them, should absolutely get immunized so that the patient can get secondary protection.

**Barry Popkin:** We can't address any of the issues concerning vaccine efficacy with cancer patients. We wish we could, but it's impossible.

8. **Do you see efficacy of the vaccine for individuals with obesity being tested and vaccine trials in this population as being possible in future, and are there plans?**

   **Barry Popkin:** The data are there. They can do it. In the U.S. and in the U.K., with 35 to 40 percent of the populations being obese, it'll be quite easy. With another 40 percent being overweight, in all the high-income countries where the tests have been done, we have such huge populations, and they'll have the data because they only excluded people with some extreme issues, like serious cancers. So, those analyses are yet to be done, and it is possible to do, in my opinion.

9. **Dr. Warner, have you done any sensitivity analyses where you exclude patients you suspect are cachexic, and do you have information about recent weight loss for your patients to better assess this?**

   **Jeremy Warner:** When I looked at those numbers, I saw those trends, and I saw, clearly, the patients with poor performance status being relatively underweight. I do think we would have to do it. It very quickly becomes obvious that even a database of 6,000 patients is not sufficient once you start dropping large portions of it. But unfortunately, I believe we'll soon be above 10,000 patients by our internal estimates. It's really a question of statistical power. We certainly wouldn't want to try to make any claims of "no association" if the power wasn't sufficient. So, it's a fine line there. Of course, there's all the caveats of retrospective cohort studies, which we cannot forget. With all that being said, I think the next step is to try to zero in on a population that isn't clearly having cancer cachexia or related issues, as I showed you on those "violin plots." I do say there's another side of that coin, which is the patients who are gaining weight because of their cancer treatment. These are patients that were not necessarily obese for years or even longer. These are people who've gained 20, 30 pounds as a result of the steroids they get for their chemotherapy. It doesn't tend to come off, though, but it's almost more of a transient obesity in this case, and I wonder how that's different.

   **Barry Popkin:** I don't think any of us can speak to that issue at this point. There are so many unknowns here.

10. **Do we know anything about obesity and COVID-19 risks in children? Have there been studies done or any data gathered?**

    **Barry Popkin:** Yes, we looked at children's data, and particularly among adolescents, there are the same effect as in adults if they're obese. We don't have

data from children under the age of 12. We don't have enough cases with preschoolers, obviously. With school-age children, the numbers are so small that I would hate for us to try to do analyses with these sample sizes. It could be done, it could give us the relationship, and you can do odds ratios, but we won't have enough of these studies from around the world. I also know from my colleagues doing clinical work in Brazil and Mexico that the number of children coming into the hospitals is minuscule compared to the adults and the adolescents, and there are very few adolescents.

11. **Dr. Warner, do you have plans to expand data collection and assessment to pediatric cancer patients?**

    **Jeremy Warner:** First of all, fortunately pediatric cancer is uncommon. I mean, it gets a lot of attention, and rightly so, but it is fairly uncommon. When you look at the intersection of an uncommon cancer with an uncommon infection among children, the numbers do get small. Additionally, for that reason, we are very sensitive to re-identification concerns. Although our database is de-identified, we've gone beyond HIPAA. We don't even disclose geographic region at the state-level when we share our information because we really are sensitive to the possibility of re-identification. So, for those reasons, we're currently not accepting reports for people under the age of 18. But I do believe the NCI prospective trial, the NCCAPS, and, perhaps some others are collecting pediatric cases. So, I hope that one of those other efforts that may have a better way of preventing any possibility of re-identification, might help us learn more.

12. **Does the COVID-19 & Cancer Consortium include cancer patients who are not diagnosed with COVID-19 or only those who have both?**

    **Jeremy Warner:** We collect presumptive cases. So, I have to say the vast majority in this country and outside are confirmed by PCR, you have SARS-CoV-2. But we will take reports of presumptive cases of COVID-19.

13. **It seems these unhealthy behavioral patterns that have been established with less physical activity and more unhealthy diets. The speculation is that will increase rates of obesity and obviously continuation of those patterns. But I'm wondering if those countries that have gotten more on top of the pandemic -- New Zealand, Australia, some of the Asian countries -- are we seeing a reversion to some of the prior patterns of behavior, and perhaps this is a temporary kind of thing? Or are we seeing, or is it too early?**

    **Barry Popkin:** First of all, the data coming from colleagues in Australia and New Zealand is that they're responding in the same ways the rest of the world is. Except now, they're back to more normal living in both countries, and Australia had a short blip when they had to be more careful in Melbourne and a few areas. Then, it's a question of what they ate before because they're working, doing everything normally in New Zealand. So, we don't know from them. We certainly know from Europe that they're functioning just like Americans, eating more junk food and beverages, being much less active, and so the situation's going to be the same. We're going to see these 10, 20, 30-pound weight gains during COVID-19 from many populations. The question is, again: Do people then go back to healthier behaviors? Perhaps we then see trends to a reduction. It is much easier to prevent weight gain than it is to lose

weight. It's purposeful, and for much of the population, I think it will be very difficult to go backwards. So, I think a year or two from now, the NHANES data are going to show us significant shifts to the right in our weight distribution (towards greater weight) and BMI distribution across the country in all ages. But we'll have food insecurity as well. So, what this has meant, if people are buying more store foods that are not perishable, that they are certainly shifting more to unhealthy foods in general. We'll have data on that later because we get 60 to 90,000 people in the country and households' daily food purchases. So, we'll know subsequently, but it will take time to understand, and it'll be too late for now (and weight gain prevention). Obviously, we don't have a government pushing toward healthy living and eating, so we're in a difficult situation that way. Only the U.K. has come out of this with active interventions to deal with weight. They've cut marketing. They've done several things during this pandemic and talked a lot about weight increases and healthy eating. That had a lot to do with Boris Johnson's weight-related complications from COVID-19 and coming out of it with that push, and he unleashed the government to do more. So, it's interesting, there will be almost a "natural experiment" in a sense to take a look at what the outcomes are there in terms of weight.

14. **There has been a trend in non-COVID-19 infected individuals during this pandemic in an increase in more aggressive, rapidly growing tumors, specifically in early-stage breast cancer presenting in stage 3. Is the COVID-19 & Cancer Consortium looking at the impact of the COVID-19 pandemic, including this increased obesity, but also stress and inactivity, on more aggressive tumor behavior?**

    **Jeremy Warner:** Unfortunately, it sounds like perhaps that may be someone who delayed screening, which is clearly a trend. Some reports have found over 90 percent decreases in the rates of elective screenings, mammograms, colonoscopies, and so forth. So, I think there's this widely anticipated and feared "upstaging," if you will, of cancers broadly. The NCI is extremely concerned about this. On the flip side of that coin, it is now starting to emerge that cancer diagnoses this year are down by half. Well, that's not because cancer went away, right? We all know that. So, I think, COVID-19 or not, people are changing their behaviors, and that includes decisions about screening or decisions to get symptoms worked on, too. So, I think that's probably what is being noted here. I think there is a separate question about whether this virus has any effect on cancer, on its pace of progression or transformation, perhaps. I don't believe there's any basic science to suggest that this is a virus with transforming potential, like much more well-known viruses that are associated with malignancy. I think time will tell for that, as well. We've gotten at least a few anecdotes that have come through our consortium about patients who may have acquired a second malignancy around the time of the virus. I don't think those anecdotes will answer that question. I do think, again, the combination of lowered screening, increased obesity, more sedentary lifestyles-- none of these things are going to be good for cancer incidence or stage when diagnosed, unfortunately.

15. **Given the known risks of both obesity and undernutrition, should weight loss be recommended in patients that are not currently infected with COVID-19?**

    **Barry Popkin:** It really depends on the subpopulation. In our country, absolutely. Actually, this also applies to most of the low- and middle-income world because the patients and individuals in urban areas have changed their diet so much to less

healthy eating that we need to find ways to deal with that. Among those who are really undernourished, they're getting special feeding, and that's preschoolers, mainly. Once you're stunted thereafter, it's a different ballgame in terms of eating. Yes, there are a few food challenges in each of our countries, and it's very different than it is in the U.S. and the higher income countries. But, again, the urban populations are gaining weight so fast that we have to talk about that.

16. **Given the phenomenon of "brain fog" in both cancer patients and long-term COVID-19 patients, has the COVID-19 & Cancer Consortium discussed the possibility of exploring potential patterns, or mechanisms? Do patients that experience this "brain fog" have increased likelihood to experience long-term COVID-19 brain fog? Could there be common mechanisms at play?**

**Jeremy Warner:** Well, I've been personally experimenting with the effects of sleep deprivation on brain fog, and spending months at a time in the same house, right? I think there are so many factors. That's a super interesting question. I have certainly seen patients whose lives have been disrupted by "chemo brain", and nobody knows why. Fundamentally, we don't understand what's going on there. The data that came out of the U.K. recovery trial was great, and I think, in the right populations, steroids are the way to go. But you can imagine someone getting high-dose steroids in an ICU on a mechanical ventilator is going to get steroid myopathy and all kinds of other issues. They will hopefully survive their COVID-19 infection, but it wouldn't be any surprise if they have long-lasting effects directly related to steroids and, possibly, the virus, such as long-term inflammation. So, we'll try to collect that data. We're not the only ones, but we're thinking of coordinating with ASCO and other organizations. We're trying to think about what is feasible and practical to collect over time, and that's certainly a great idea.