Obesity and Prostate Cancer Risk: Gaps in our Current Understanding, and Thoughts on How to Close the Gaps

Q&A Session

This document features panelists' answers to relevant attendee questions that were not answered during the webinars.

Part 1: February 28, 2023
Part 2: March 24, 2023

PART I – STEVE J. FREEDLAND, MD, AND MARIAN L. NEUHOUSER, PhD, RD

1. **Q: What is the most promising biologic avenue of research that scientists should investigate?**

   A: S. Freedland: If I had to bet, I would bet on first and foremost that it is the cumulative effect of multiple pathways. However, if I had to bet on one single pathway, I would argue for insulin/insulin-like growth factor (IGF) pathways and inflammation. I think increased cholesterol and alterations in sex steroids may play a role too, but chronic inflammation and hyper-insulinemia are probably our strongest bets at this point.

   M. Neuhouser: I agree that it is likely multiple pathways because interrogation of single mechanisms has yielded inconsistent results. It may also be worthwhile to examine new exposures – particularly those that might be experienced by men who are diagnosed with more aggressive disease and among Black men. Little has been done on occupational exposures, geospatial epidemiology, Per- and polyfluoroalkyl substance (PFAS)/other chemicals, and the like.

PART II – EDWARD GIOVANNUCCI, MD, ScD, AND MICHAEL POLLAK, MD

1. **Q: Skeletal muscle is a component of body composition that increases on average with BMI and is important to insulin resistance: how does this enter interact with the roles of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) that you have outlined as important to the BMI-prostate cancer risk story?**

   A: E. Giovannucci: It is true that skeletal mass increases proportionally as adiposity increases in reasonably healthy, not elderly individuals. This relationship is why BMI is useful at all, especially in young, reasonably healthy individuals. Because of the high correlation between fat mass and lean mass, BMI correlates fairly well with fat mass. However, in situations where lean mass and fat mass are less associated, BMI is less predictive. This can arise in sarcopenia or in individuals with relatively low body weight (lean mass) yet fairly high fat mass (often, in this case, fat mass will be VAT). Loss of skeletal mass is a poor prognostic indicator. It is less clear though how this would relate to risk of prostate cancer.

2. **Q: How does visceral versus subcutaneous fat, BMI, and height-weight ratio (HWR) differ among various racial/ethnic groups, and can it be directly correlated with aggressive forms of prostate cancer seen among the African American population? Should these factors be taken into consideration along with polygenic risk prediction model generation for various racial/ethnic groups?**

A: E. Giovannucci: Asian populations tend to have the highest proportion of VAT compared to SAT, but overall, less adiposity. The African American population tends to have higher body fat overall, but not disproportionally high VAT. Adiposity does probably contribute to aggressive prostate cancer overall, but I don't think it is the driver of racial/ethnic differences. In the standard polygenic risk scores for prostate cancer risk, adiposity-related genes do not seem to be very important. This doesn't mean that adiposity is not important. The combined effect of many genes (hundreds) contributes to BMI. It would be interesting to examine the interaction of polygenic risk for obesity and polygenic risk for prostate cancer in various racial/ethnic groups. To my knowledge, this has not been done.

3. **Q: Exercise is insulin-lowering (possibly fat reducing and muscle building, if vigorous enough) and I am interested in hearing the panel's views about exercise.**

   A: E. Giovannucci: Although few modifiable risk factors can be said to be firmly established for prostate cancer, vigorous exercise seems to be one of the more promising, at least suggestive, for aggressive prostate cancer. This finding would be consistent with the insulin and possibly inflammation lowering effects of exercise.

   M. Pollak: Although I do not believe definitive data prove the point, it would be expected that exercise via insulin lowering would be beneficial to patients. Research in this field is difficult in part because patients able to exercise are likely to be healthier at baseline and may have better outcomes that are not a consequence of exercise.

4. **Q: Are there any prostate specific markers for insulin action in patients with obesity?**

   A: E. Giovannucci: I'll defer to Dr. Pollak, but Dr. Pollak did show a study we did in the Physicians' Health Study that showed men with obesity and a high C-peptide level (marker of insulin resistance and secretion) had worse outcomes if they had prostate cancer. Insulin-like growth factor (IGF1) does definitively predict risk of prostate cancer (though IGF1 is not the same as insulin action, they do have overlapping pathways).

   M. Pollak: There are no prostate-specific markers. In prostate tissue, like others, insulin leads to increases in PI3K (phosphatidylinositol-3 kinase) pathway activity which can be detected by IHC (immunohistochemistry).

5. **Q: Are there citations for bariatric surgery reducing cancer risk?**

   A: E. Giovannucci: Bariatric surgery clearly has reduced risk of cancer in women, driven by endometrial and breast cancer. The effect of obesity on these cancers occurs at very late stages of the disease, so a reversal of adiposity-associated risk could be seen in a few years. For other cancers, the evidence is not as clear, but this could be due to lower numbers and perhaps a longer time required for an effect. To my knowledge, there is no firm supportive data for prostate cancer.

   M. Pollak: Yes, there are several. If you look at PubMed and search "bariatric surgery" and "cancer," they are easy to find and rather impressive.

6. **Q: Are you looking at the Ketogenic Diet to recommend reducing hormonal influence?**

   A: S. Freedland: We have done a series of studies focused on low-carbohydrate diets (Carbohydrate and Prostate Studies (CAPS); CAPS1 and 2; PMID 35486445, 35338353, 34259565, 33949711, 33819069, 32108029, 30664736). Collectively, we found that these diets induce significant weight loss (~20 pounds in 6 months), blunt the metabolic effects of hormonal therapy, and in a post-hoc exploratory analysis may slow the rate of prostate-specific antigen (PSA) increases in men with recurrence prostate cancer. Thus, while more research is needed, I am recommending these diets, with appropriate caveats, to patients. I also clearly explain to patients that our studies were compared to the Western diet, not other diets that have been purported to be healthful for cancer (i.e., Mediterranean, or whole food plant-based). Thus, I make no claims that a low-carb diet is the "best" diet, but rather I review what our studies found.

   M. Pollak: Ketogenic diets are hard to maintain over the long term. The decrease in insulin would be expected to be beneficial. However, an easier diet involving low levels of simple sugars might have similar effects and be easier to maintain.

7. **Q: Is there any relationship between the prevalence of cancer in general and dairy product consumption? What about the relationship with other types of cancers, especially in children?**

   A: S. Freedland: There is some evidence that dairy may increase prostate cancer, though the studies are not conclusive. It may be related to some of the complexities of the endpoint (aggressive, advanced, total, fatal prostate cancer, etc.). For other cancers, there is no strong evidence, except for a protective association for colorectal cancer, likely due to calcium. A big gap is studies in children; there is very little study of this.