Adolescent Obesity and Inflammation in Relation to Colorectal Cancer Risk: Recent Findings and Future Implications

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Childhood Obesity: *Is the connection between higher body mass index (BMI) and colorectal cancer risk in adults solidly defined at this point?*

Dr. Kantor: The positive association between BMI in adulthood and risk of colorectal cancer is fairly consistent in the literature. Interestingly, the association between adult obesity and colorectal cancer seems to be stronger among men than women. While this could be due to differences in hormones, the underlying reasons for this pattern of association are not entirely clear.

Dr. Giovannucci: In adults, there have been many studies on adult BMI and risk of colorectal cancer—I believe there are well over 50 studies now. These studies have been summarized in meta-analyses, and these meta-analyses indicate a positive association between adult BMI and risk of colorectal cancer. There are some that show the association is stronger in men. But it is there for women, too.

In several studies, the association is stronger in premenopausal women, and then it weakens a bit in postmenopausal women, and we do not know why that is. But as Dr. Kantor suggested, it might be related to hormones. For example, in postmenopausal women, obesity is associated with higher estrogen levels, and there is some evidence that estrogens may be protective against colon cancer, so the women may be getting some benefit from the estrogens.

CO: *You were both on the author team of a recently published study¹ looking at BMI and adolescents' colorectal cancer risk (CRC). Could you discuss why you decided to take on this missing component in current literature?*

Dr. Kantor: While we know a lot about adult obesity and colorectal cancer, we know less about the association between adolescent obesity and the risk of colorectal cancer.

With colleagues in Sweden, we were able to use existing Swedish registry data to evaluate the association between measured adolescent BMI and risk of CRC in a large cohort of men conscribed in the Swedish military between 1969 and 1976.

The fact that BMI was measured in this study is important because recall of adolescent BMI is imperfect, and any degree of error can diminish our ability to see associations.

More importantly, since we had such a large cohort study, with almost 240,000 men, we were able to disaggregate adolescent obesity from adolescent overweight, and were able to further break up the overweight group into two groups, lower overweight and upper overweight. In a smaller study, we couldn't have done that, because in the '60s and '70s, we did not have nearly as many overweight and obese adolescents as we have today.

CO: *Did the large data set on adolescent males guide your choice for an all-male cohort or might you have focused on this group regardless given what you know about the association in adult men?*

Dr. Kantor: We were able to examine the association between adolescent obesity and risk of colorectal cancer because adolescent height and weight were collected on men conscribed in the Swedish military, and this information was recorded in the national conscription registry. As conscription was mandatory for men at this time in Sweden, we had data on adolescent BMI for almost the entire male adolescent population, which is wonderful. However, we did not have data on women and were therefore unable to include them in the study. In the ideal world, we would do this study among women, as well.

CO: *Could you discuss how strong you felt the link was between BMI and colorectal cancer risk in your findings?*

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Dr. Kantor: The results were very strong. We observed that men in the upper overweight group—men with a BMI between 27.5 and 30—had about a 2.08-fold higher risk of colorectal cancer, and obese men had a 2.38-fold higher risk of colorectal cancer than their normal-weight counterparts. Those are really strong associations.

We have to consider the fact that we do not have data on all potential confounders, like smoking and diet, because this is a registry-based study. We were therefore unable to adjust for all of those factors. Even so, with such strong hazard ratios, it is unlikely that those variables account for the entirety of the observed association between adolescent BMI and risk of colorectal cancer.

Dr. Giovannucci: When you see associations like this—with hazard ratios between 2 and 2.5—even after adjustment for confounders, associations with that strength do not go away entirely. They might get attenuated a little bit. The associations we found with adolescent BMI and colorectal cancer risk are so strong that we do not think that confounding by other factors accounts for the observed associations.

CO: *Could you outline how systemic inflammation in overweight teens may contribute to increased cancer risk?*

Dr. Kantor: We know that inflammation during adulthood is implicated in the etiology of colorectal cancer, but we know little about how inflammation in early life may affect risk of colorectal cancer. To our knowledge, this is the first study to examine the association between adolescent inflammation and risk of colorectal cancer.

In our study, we did see an association between adolescent inflammation and colorectal cancer; notably, this association was independent of obesity.

Here, we have the same issue that we discussed earlier—adolescent inflammation could be correlated with adult inflammation, and we cannot say at which time point inflammation might be more relevant to the development of the cancer because we do not have measures in adulthood. Further research is needed in this area.

CO: *Does this research establish cause and effect or just suggest the possibility of it?*

Dr. Kantor: I think that it is certainly suggestive, but this is a single epidemiologic study in a relatively young area of study. This is an area of research which is growing, and further studies are needed to understand if adolescent obesity is causally associated with colorectal cancer, or if it is just associated due to correlation with adult obesity.

Dr. Giovannucci: Yes, I agree. These are exciting studies, but they are limited in scope at this point.

I just want to make one point in terms of the relationship between adolescent obesity and adult obesity, and the causal link. Biologically, we do not know when the link

begins between obesity and cancer. But it is important to note that even if the link is not until adulthood, in most populations, there will be a correlation between childhood obesity and adult obesity. Once the process of obesity starts, it is hard to reverse.

So in that sense, you could argue that it is at least a causal association in the sense that childhood obesity is one of the causal factors for adult obesity. So, in other words, in most populations we could likely expect that if you have more adolescent obesity, you likely will have more colorectal cancers in the long run. It remains to be seen whether the effect is directly from the adolescent obesity or just that the adolescent obesity is likely to lead to obesity during adulthood.

CO: *With obesity more prevalent in younger people, will the onset of colorectal cancer also come on earlier in life?*

Dr. Giovannucci: It is true that, at least in the United States, early onset colorectal cancer—before the age of 50—is increasing in incidence. And there is no clear explanation. We do not think it is just due to detection bias. So there probably is a true increase in early onset cancers, and there are most likely many risk factors involved.

One of the potential explanations for the increase in early onset colorectal cancer is the increased prevalence of childhood/adolescent obesity, but we cannot say definitively at this point.

CO: *Is there anything about your findings that surprised you?*

Dr. Kantor: I think that the strength of association between BMI and colorectal cancer did surprise me a bit. I also found it interesting that the association between adolescent obesity and risk of colorectal cancer did not attenuate with adjustment for erythrocyte sedimentation rate, our measure of inflammation. This was interesting because inflammation is one of the potential mechanisms by which obesity could affect risk of colorectal cancer. This may indicate that the association between adolescent obesity and risk of colorectal cancer is working through a mechanism independent of adolescent inflammation. However, at the same time, erythrocyte sedimentation rate is just one marker of inflammation, and there are a whole host of markers of inflammation. It could still be that adolescent obesity does affect colorectal cancer risk through an inflammatory mechanism, just not marked by this particular biomarker of inflammation. But even so, I thought it was interesting.

Dr. Giovannucci: We did not know what to expect. It was interesting to see that there was an association with inflammation at this early age. In one sense, what is surprising for inflammation: we do see an effect closer to the time of diagnosis. We know that, for example, if you take aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in adulthood, you do see a reduction in colorectal cancer

within about ten years or so. So we know that it is at least acting relatively late, but we never had a sense whether higher inflammation earlier would be associated with risk. So it was kind of surprising in that sense.

Dr. Kantor: Inflammation is just one potential mechanism. There are also insulin-related pathways, sex steroids, and adipokines. This is to say that there are various mechanisms by which obesity could affect colorectal cancer, and inflammation is just one of them.

Dr. Giovannucci: Yes, that is a good point. Obesity is associated with many metabolic abnormalities, and there have been studies, for example, that have directly linked high levels of insulin, even controlling for obesity, with risk of colorectal cancer. So there are other mechanisms beyond inflammation that would suggest a link.

CO: *What would you like to see from future research to inform this field?*

Dr. Kantor: Although we do not think that factors like smoking and diet could account for the strength of association observed, it would still be ideal to be able to account for these factors. I also think looking at these associations in women would be informative.

Most importantly, however, we would like to have measures of obesity at other points in the life course, as this can help us figure out at what point body mass index may be most relevant to the development of colorectal cancer.

Without those life course measures, we are unable to isolate BMI in adolescence from BMI at other time points in the life course. Without this data, we can't speak to whether weight loss during adulthood might mitigate the risk associated with adolescent obesity. However, I should note that there was a study published around the same time as our study in which study authors found that men who lost weight over adulthood experienced lower risk of colorectal cancer than those men who did not lose weight.²

Dr. Giovannucci: The findings related to obesity and inflammation are certainly important, but we are thinking, in general, that a lot of the risk factors for colorectal cancer and probably many other cancers are important in adolescence and in childhood. Most studies have focused on adult risk factors; for example, most cohort studies, such as the Nurses' Health Study, started in adults.

In another study, we started to look at diet in adolescence, and we are starting to see associations with colorectal adenomas, which are precursors to cancer. In these studies, we have found that the Western diet during adolescence seems to be associated with increased risk. Further, we have indication that fruit and vegetable intake during adolescence may be beneficial in reducing risk.

Cancer is a long process. In colorectal cancer, the average age of diagnosis is in the 60s, but you actually start seeing precursor lesions decades earlier. This study gives us a little more indication that lifestyle factors are important and beginning very early in life, which has important public health implications.

Dr. Kantor: If adolescence, or early life, offers an etiologically relevant period for the development of colorectal cancer, then intervening in adulthood could be potentially intervening later than we should be. Life course studies are going to be important for moving forward.

CO: *Do you have any closing thoughts on this increasingly important topic?*

Dr. Giovannucci: People do not often think of cancer as an effect of obesity. Most people know the connection to diabetes, blood pressure, and heart disease. Sometimes cancer makes a bigger impression on people in terms of something to avoid. Obesity is becoming one of the more important causes of cancer, and probably as smoking rates go down, it may overcome smoking numerically as a major cause of cancer in general.

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—Jamie Devereaux, Features Editor