# The Role of Obesity as a Risk Factor for Early-Onset Cancers

## June 16, 2025, 12:00 – 1:00 p.m., ET

## Webinar Questions and Answers

1. **Is there a best practice on how to get younger populations screened for colorectal cancer when insurances typically only cover screenings based on guidelines?**

*For those with insurance, this may require prior authorization and peer-to-peer meetings to justify the colonoscopy. There are also financial resources through the Colorectal Cancer Alliance and American Cancer Society.*

2. **Are there any tests or assays being developed or available that can check for gut microbiome balance in healthy people? If an imbalance is detected can this be addressed by diet, supplement or fecal transplants perhaps**

*Yes, there are several tests and assays available that assess gut microbiome balance in healthy individuals, and if imbalances (dysbiosis) are detected, there are multiple ways to address them. The main interventions are dietary interventions (fiber, reducing processed foods) and probiotics or prebiotics. Fecal transplants are also being investigated but are not ready for broad applications at this time.*

3. **While obesity may lead to increased risk, how is this offset by the improved response to therapy due to less cachexia?**

*Paradoxically, mild to moderate obesity may confer a survival advantage during cancer treatment, a phenomenon sometimes referred to as the "obesity paradox." This may impact response to cancer therapy, but still, obesity is associated with a greater risk of developing the cancer.*

*This is an area that needs more research. There is also evidence that obesity may shorten survival, particularly for pancreatic cancer, however this might be related to people with adiposity being diagnosed with later stage of disease. In addition, visceral adiposity in mice has been linked to shorter pancreatic cancer survival because of its proinflammatory environment and altered metabolic pathways.*

4. **Is there a relationship between GLP1RAs (GLP1 receptor agonists; anti-obesity drugs) have shown any effects on the occurrence of colorectal cancer?**

*Yes, recent research suggests that glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), a class of drugs used to treat obesity and type 2 diabetes, may be associated with a modestly reduced risk of colorectal cancer (CRC), particularly in individuals with obesity and diabetes.*

*There were some early studies that suggested the GLP-1 class drugs increased the risk of pancreatic cancer because of their side-effect of pancreatitis. More recent research has suggested protective associations.*

5. **For Dr. Lieu, thank you for laying out a great call to action list. If a statewide coalition is working on colorectal cancer efforts, where would you advise they "start" with their efforts as it relates to early age onset colorectal cancer?**

*There are a lot of ways to start, but one place to start would be to establish a statewide "task force", launch a public awareness campaign, identify and improve barriers to screening access, and support provider education about early-onset cancers.*

6. **Dr. Lieu, is there an explanation for the difference in the chances of developing colorectal cancer between living in the suburbs and urban and rural areas?**

*While not totally known, likely key contributing factors include, lower screening rates, limited access to specialists and diagnostic serves, longer travel distances to care, and high rates of some risk factors such as smoking and obesity.*

7. **How is obesity or unhealthy BMI applicable when there are people who may physically be overweight, but they eat healthy and workout 5-6 days a week but due to hereditary genes it makes it harder for them to lose weight?**

*You're absolutely right, body weight alone doesn't tell the full story of a person's health, especially when genetics, lifestyle, and metabolic health are considered. While not all people with obesity are unhealthy, obesity is still associated with increased risk for conditions like colorectal cancer, type 2 diabetes, and cardiovascular disease, especially when accompanied by visceral fat, inflammation, or insulin resistance. The key is to individualize risk assessment rather than rely solely on BMI.*

*Height is also a consistent risk factor for pancreatic cancer. BMI or waist to hip circumference are better measures of adiposity than body weight alone. For example, taller people weigh more than shorter people and comparing their weight will not help with examining adiposity. More research is needed to examine hereditary genes, weight loss and pancreatic cancer.*

8. **Adults who lose weight with diet and exercise changes are rarely able to sustain this weight loss for longer than about 5 years. What is the role of other interventions in helping overweight/obese people sustain weight loss long-term?**

*This is something that is very difficult to examine with respect to cancer and would require a very large, randomized trial to truly answer. We have examined weight loss and negative BMI change with pancreatic cancer which has shown increased risk, however, is likely due to reverse causation.*

9. **Can you speak about visceral fat and increased risk of cancer?**

*We have hypothesized that the positive BMI associations for pancreatic cancer are due to visceral fat. Mouse studies have linked visceral adiposity to pancreatic cancer. In addition, visceral adiposity in mice has been linked to shorter pancreatic cancer survival because of its proinflammatory environment and altered metabolic pathways.*

10. **Is there any role of metformin in prevention of pancreatic cancer, especially when it helps in alleviating insulin resistance?**

*The results from epidemiologic studies for metformin preventing pancreatic cancer are **not** consistent. Some studies have shown protective associations, however, have had limitations in their design study. The issue is that diabetes is also a symptom of pancreatic cancer and diabetes due to subclinical disease is difficult to control with metformin, so these patients are often treated with other diabetes medications like insulin.*

11. **The occurrence of colorectal cancer increased from 1950 to current time point. Can it also be related to food and diet? Can less fiber and more processed food increase the risk of colorectal cancer? Can changes in diet change the outcome of cancer?**

*Yes, there is strong and growing evidence that dietary patterns, especially low fiber intake and high consumption of processed foods, are significantly linked to the rise in colorectal cancer, particularly in younger adults.*

*Healthy or greater dietary quality has been associated with reduced pancreatic cancer risk in epidemiologic studies.*

12. **Does gestational diabetes impact occurrence of pancreatic cancer later in life? [even if the mother was very thin?]**

*There have been few studies that have examined this. They are very small (i.e. 54 cases or case-reports of pancreatic cancer being diagnosed when someone is pregnant). More research is needed to answer this question.*

13. **What is the method of pancreatic screening for high risk people?**

*Only people with a high family risk and with known familial mutations are recommended for screening.*

*Below are the recommendations from the AGA:*
*"CLINICAL PRACTICE ADVICE*

*Pancreas cancer screening should be considered in patients determined to be at high risk, including first-degree relatives of patients with pancreas cancer with at least two affected genetically related relatives.*

*Pancreas cancer screening should be considered in patients with genetic syndromes associated with an increased risk of pancreas cancer, including all patients with Peutz–Jeghers syndrome, hereditary pancreatitis, patients with CDKN2A gene mutation, and patients with one or more first-degree relatives with pancreas cancer with Lynch syndrome, and mutations in BRCA1, BRCA2, PALB2, and ATM genes.*

*Genetic testing and counseling should be considered for familial pancreas cancer relatives who are eligible for surveillance. A positive germline mutation is associated with an increased risk of neoplastic progression and may also lead to screening for other relevant associated cancers.*

*Participation in a registry or referral to a pancreas Center of Excellence should be pursued when possible, for high-risk patients undergoing pancreas cancer screening.*

*Clinicians should not screen average-risk individuals for pancreas cancer.*

*Pancreas cancer screening in high-risk individuals should begin at age 50 years, or 10 years younger than the initial age of familial onset. Screening should be initiated at age 40 years in CKDN2A and PRSS1 mutation carriers with hereditary pancreatitis and at age 35 years in the setting of Peutz–Jeghers syndrome.*

*Magnetic resonance imaging and endoscopic ultrasonography (EUS) should be used in combination as the preferred screening modalities in individuals undergoing pancreas cancer screening.*

*The target detectable pancreatic neoplasms are resectable stage I pancreatic ductal adenocarcinoma and high-risk precursor neoplasms, such as intraductal papillary mucinous neoplasms with high-grade dysplasia and some enlarged pancreatic intraepithelial neoplasias.*

*Screening intervals of 12 months should be considered when there are no concerning pancreas lesions, with shortened intervals and/or the performance of EUS in six to 12 months directed towards lesions determined to be low risk (by a multidisciplinary team). EUS evaluation should be performed within three to six months for indeterminate lesions and within three months for high-risk lesions, if surgical resection is not planned. New-onset diabetes in a high-risk individual should lead to additional diagnostic studies or change in surveillance interval.*

*Decisions regarding therapy directed towards abnormal findings detected during screening should be made by a dedicated multidisciplinary team together with the high-risk individual and their family. Surgical resection should be performed at high-volume centers.*

*Clinicians should consider discontinuing pancreas cancer screening in high-risk individuals when they are more likely to die of non-pancreas cancer–related causes due to comorbidity and/or are not candidates for pancreas resection.*

*The limitations and potential risks of pancreas cancer screening should be discussed with patients before initiating a screening program."*

14. **Is there an association with a family history of obesity and a family history of early-onset cancer?**

*Mendelian randomization studies that used known single-nucleotide polymorphisms (SNPs) that are associated with obesity have demonstrated positive associations with pancreatic cancer. Yes, there is evidence to support family history of obesity and pancreatic cancer risk, however it is uncertain whether this is associated with early onset cancer.*

15. **How does mitochondrial stress in obesity affect the development of cancer?**

*Obesity can increase oxidative stress which can damage mitochondrial DNA. Mutations or damage to mitochondrial DNA (mtDNA) can alter the subunits of the electron transport chain, a key part of mitochondrial energy production. This can lead to further dysfunction and the promotion of a pro-carcinogenic environment.*

16. **What are the potential association with germline predisposition? Will it be gene specific or cancer type specific?**

*There are genome-wide association studies (GWAS) that have identified common germline SNPs associated with pancreatic ductal adenocarcinoma. To date 20 SNPs have been identified in people of European ancestry. There have also been familial studies that have identified SNPs related to familial syndromes. The later include Peutz–Jeghers syndrome, hereditary pancreatitis, patients with CDKN2A gene mutation, Lynch syndrome, and mutations in BRCA1, BRCA2, PALB2, and ATM genes.*

17. **Is there a link between obesity and childhood pancreatic cancer?**

*Pancreatic cancer in childhood is very rare and has not been studied.*

18. **What is the current recommendation of percentage weight loss that has meaningful reduction in cancer risk? Thoughts on "food swamps" & cancer.**

*This area needs more research. For pancreatic cancer weight loss has been associated with increased risk, likely because of reverse causation.*

19. **What are the anatomic and molecular differences between early and late onset of colorectal cancer?**

*We know that early-onset colorectal cancers are more likely to be poor differentiated and have slightly more aggressive histology. There are also minor differences in the rate of certain mutations, such as KRAS, BRAF, and APC mutations. Early onset cancers are also more common in the distal colon and rectum.*

20. **What do you see as the role of oral health for potential impact for both obesity and cancer (what is needed to demonstrate oral health involvement)?**

*Tooth loss and periodontal disease has been associated with greater pancreatic cancer risk, however the impact with obesity has not been well studied.*

21. **How is obesity linked to cancer given that weight and body fat can be influenced by conditions like Polycystic Ovary Syndrome or genetics, not just lifestyle?**

*Overweight and obesity have been associated with pancreatic cancer. Mendelian randomization studies that have used known obesity GWAS SNPs have shown associations with elevated with pancreatic cancer. So, both lifestyle and genetics play a role in the obesity association with pancreatic cancer.*

22. **Are cancer-related risk factors different between metabolically healthy vs. metabolically unhealthy obese patients?**

*Yes, cancer-related risk factors are different between metabolically healthy and metabolically unhealthy obese patients, though the relationship is complex. Research consistently shows that being metabolically unhealthy, regardless of a person's weight, significantly increases the risk of certain cancers. However, obesity itself, even in the absence of metabolic abnormalities, is also an independent risk factor. Specifically, the increased cancer risk is driven by insulin resistance and hyperinsulinemia, chronic inflammation, and hormonal dysregulation.*

**23. Opinion regarding cancer risk in individuals using GLP-1 inhibitors and maintaining weight loss?**

*There were some early studies that suggested the GLP-1 class drugs increased the risk of pancreatic cancer because of their side-effect of pancreatitis. More recent research has suggested protective associations between GLP-1 antagonists and pancreatic cancer.*