RESEARCH
Narrative Review

Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer

Guido Eibl, MD; Zobeida Cruz-Monserrate, PhD; Murray Korc, MD; Maxim S. Petrov, MD, PhD, MPH; Mark O. Goodarzi, MD, PhD; William E. Fisher, MD; Aida Habtezion, MD; Aurelia Lugea, PhD; Stephen J. Pandol, MD; Phil A. Hart, MD; Dana K. Andersen, MD; on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

ARTICLE INFORMATION

Article history:
Submitted 19 April 2017
Accepted 10 July 2017

Keywords:
Pancreatic cancer
Obesity
Type 2 diabetes mellitus
Prevention
Review

http://dx.doi.org/10.1016/j.jand.2017.07.005

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest types of cancer. The worldwide estimates of its incidence and mortality in the general population are eight cases per 100,000 person-years and seven deaths per 100,000 person-years, and they are significantly higher in the United States than in the rest of the world. The incidence of this disease in the United States is more than 50,000 new cases in 2017. Indeed, total deaths due to PDAC are projected to increase dramatically to become the second leading cause of cancer-related deaths before 2030. Considering the failure to date to efficiently treat existing PDAC, increased effort should be undertaken to prevent this disease. A better understanding of the risk factors leading to PDAC development is of utmost importance to identify and formulate preventive strategies. Large epidemiologic and cohort studies have identified risk factors for the development of PDAC, including obesity and type 2 diabetes mellitus. This review highlights the current knowledge of obesity and type 2 diabetes as risk factors for PDAC development and progression, their interplay and underlying mechanisms, and the relation to diet. Research gaps and opportunities to address this deadly disease are also outlined.
J Acad Nutr Diet. 2017;■:■-■.

IT IS ESTIMATED THAT ABOUT ONE-THIRD OF CASES OF cancer, the second leading cause of death in the United States, are caused by dietary factors.[1,2] Among the deadliest types of cancer has been and still is pancreatic ductal adenocarcinoma (PDAC), the most common histologic type of pancreatic cancer. The worldwide estimates of its incidence and mortality in the general population are eight cases per 100,000 person-years and seven deaths per 100,000 person-years, and they are significantly higher in the United States than in the rest of the world.[3] The projected incidence of this disease in the United States is more than 50,000 new cases in 2017 and it is currently the third leading cause of cancer mortality in both men and women.[2] Despite advances in understanding the biology of PDAC, molecularly targeted therapy (such as epidermal growth factor receptor inhibitors) has not translated into substantially improved prognosis. Indeed, total deaths due to PDAC are projected to increase considerably to become the second leading cause of cancer-related deaths before 2030.[4] Considering the failure to date to efficiently treat existing PDAC, increased effort should be undertaken to prevent this disease. Consequently, the focus of research has shifted gradually toward its prevention and interception, which encompasses halting transformed cells from becoming malignant cancers.[5-9] In this context, a better understanding of the risk factors leading to PDAC development is of great importance to identify and formulate preventive and interceptive strategies and to ultimately educate the public. Large epidemiologic and cohort studies have identified risk factors for the development of PDAC,[10-13] including obesity and type 2 diabetes mellitus (T2DM). This review highlights the current knowledge of obesity and T2DM as risk factors for PDAC development and progression, their interplay and underlying mechanisms, the relation to dietary influences, as well as outlines research gaps and opportunities to address this deadly disease.

EPIDEMIOLOGY OF OBESITY, T2DM, AND PDAC

Obesity and Diabetes as Risk Factors for PDAC

T2DM and obesity are among the small number of known modifiable risk factors for PDAC. There is a complex relationship between T2DM and obesity because they often coexist, but independently increase the risk for developing PDAC. An association of PDAC with T2DM and obesity is strongly suggested when the geographic prevalence of all three diseases is examined (Figure 1). The epidemiologic support for and proposed mechanisms of increased risk for PDAC in both longstanding T2DM and new-onset DM have been previously reviewed,[14-17] so the connection with obesity is further emphasized here.

Epidemiologic evidence from various study types has consistently shown that obesity is a dose-dependent risk factor for the development of PDAC.[18-24] In a population study of more than 900,000 adults, a 52% increased death rate from all cancers was observed in men and a 62% increased death rate in women with a body mass index (BMI)

>40 compared with normal-weight control subjects.[21] The relative risk (RR) of PDAC for subjects with BMI >40 was 2.61 (95% CI 1.3 to 5.4; *P*=.001) for men and 2.76 (95% CI 1.74 to 4.36; *P*=.001) for women. In addition, an increased BMI was associated with an increased risk of death from several other cancers (such as of the esophagus, liver, and colon)[25-27] in which T2DM is less prevalent, supporting an independent role of obesity in cancer development. It is important to acknowledge that the effect size of obesity as a PDAC risk factor is likely diluted when only BMI is considered because the distribution of fat appears to also influence cancer risk. For example, an increased waist-to-hip ratio is associated with a >70% increased risk of PDAC.[23]

Evidence from clinical studies shows that weight loss, induced by dietary restriction, exercise, or bariatric surgery, reduces risk of cancer.[28-33] Adams and colleagues[31] reported that the incidence of obesity-related cancers decreased by 50% in 6,596 bariatric surgery patients compared with 9,442 obese controls followed for an average of 12.5 years. Similarly, in the Swedish Obesity Subjects study involving 2,010 bariatric surgery patients and 2,037 unoperated control patients, Sjöström and colleagues[29,33] reported that the overall mortality was reduced by 24% in the surgery cohort, but the number of deaths from individual cancers was too small to assess organ-specific effects.

Interaction of Obesity with Diabetes and PDAC

Although many epidemiologic studies have been confounded by the frequent coexistence of T2DM in the obese groups, larger studies indicate that obesity confers a significant cancer risk independent of the presence of T2DM. For example, Jiao and colleagues[34] studied a pooled cohort of more than 900,000 subjects in which there were 2,454 who developed PDAC. The incidence of PDAC increased by 19% in the group with a BMI of 30 to 35, and was not influenced by the presence of T2DM.

Studies probing the contribution of metabolic alterations associated with obesity have corroborated the risk and suggest that increased insulin levels due to the insulin resistance of obesity are an important factor. Stolzenberg-Solomon and colleagues[35] studied levels of glucose and insulin and measures of insulin resistance in 29,133 Finnish male smokers followed for almost 2 decades. Fasting glucose, insulin levels, and insulin resistance (estimated with homeostatic model assessment of insulin resistance) were positively associated with PDAC. The RR of PDAC was 2.71 (95% CI 1.19 to 6.18; *P*=.006) in subjects with the highest quartile of insulin resistance. Because obesity is associated with insulin resistance in virtually all subjects, hyperinsulinemia is believed to

RESEARCH SNAPSHOT

Research Question: What is the current research on the link between obesity, type 2 diabetes mellitus, dietary issues, and pancreatic cancer?

Key Findings: This narrative review describes a clear epidemiologic association between obesity, type 2 diabetes mellitus, and pancreatic cancer risk. Major pathophysiologic mechanisms underlying this link, including inflammation and adipose tissue dysfunction, are discussed. Available animal models that study the influence of these risk factors on pancreatic cancer development are summarized, and research gaps and opportunities to advance the field are presented.

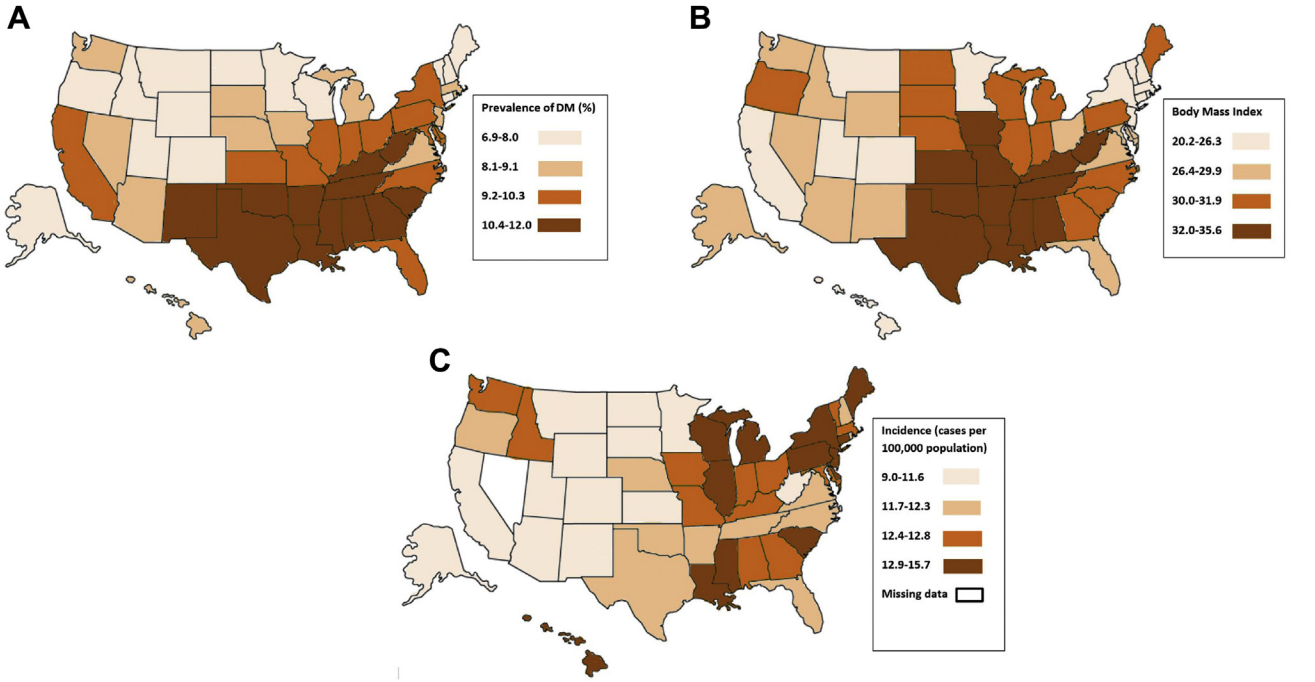

Figure 1. (A) Prevalence of diabetes mellitus (in quartiles) 2014 (from http://www.cdc.gov/diabetes/data). (B) Prevalence of obesity expressed as body mass index (in quartiles) 2015 (from http://www.cdc.gov/obesity/data). (C) Incidence of pancreatic cancer, age adjusted, in all races (in quartiles) 2009-2013 (from http://statecancerprofiles.cancer.gov/data-topics/incidence.html).