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Editorial

EDITORIAL

Mendelian Randomization Analysis Identifies Body Mass Index and Fasting Insulin as Potential Causal Risk Factors for Pancreatic Cancer Risk

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In this issue of the Journal, Carreras-Torres and colleagues present evidence for a potential causal role of body mass index (BMI) and fasting insulin with risk of pancreatic cancer in 7110 cases and 7264 controls (1). Specifically, genetically increased levels of BMI and fasting insulin were associated with an increased risk of pancreatic cancer; the association with fasting insulin was limited to men. No evidence of a causal association was observed for type II diabetes, fasting glucose, glucose at two hours postchallenge, height, waist-to-hip circumference ratio, and four lipids (eg, total cholesterol, high- and low-density lipoprotein cholesterol, and triglycerides).

Pancreatic cancer is one of the most lethal malignant neoplasms worldwide (2). Although few modifiable risk factors have been prospectively associated with risk of pancreatic cancer, the causes of the disease are still insufficiently known (3). There are no current screening recommendations for pancreatic cancer; thus primary prevention is of utmost importance. A better understanding of the etiology is essential for the primary prevention of this disease. The current paper by Carreras-Torres et al. is important because it provides additional evidence for a potential causal association between two modifiable risk factors and risk of pancreatic cancer using Mendelian randomization (MR).

MR aims to improve causal inference in observational studies by assessing risk associations of the genetically determined component of environmental exposures and intermediate phenotypes (4,5). Observational studies are prone to various biases that can distort causal associations, whereas MR may circumvent biases, such as confounding, reverse causation, and exposure measurement error because genes are randomly assorted during gamete formation and conception. MR is seeing widespread application in the field of epidemiology, and recent studies have identified a number of potential causal associations between obesity and related metabolic traits with several cancers (6–9).

Several caveats should be considered for accurate interpretation of the study findings. The assessment of statistical significance in the current MR study should have included perhaps adjustment for multiple testing as several metabolic traits were examined in relation to risk of pancreatic cancer, including associations in subgroups. Although a large sample of pancreatic cancer cases and controls was used, the statistical power for most of the associations, except for type II diabetes, was not optimal to observe the weak relative risks seen in published large meta- or pooled analyses of epidemiological studies (1,10,11). Although the authors used as genetic instruments only variants that have been associated with the studied traits at a genome-wide statistical significance level, the selected genetic variants explained together a small proportion of the variance in the different metabolic traits: 1.5% for fasting insulin, 2.7% for BMI, 5% for type II diabetes, and 10% as the lower threshold for lipids (1). Given that many of these metabolic traits are highly heritable, further work using additional genetic variants as instruments, when they become available from future genome-wide association studies, will increase power and will allow investigations in subgroups.

There are strong assumptions that must be satisfied when using MR to make causal inference, which the authors have made great efforts to assess. As the number of genome-wide statistically significant genetic variants used in MR studies increases, diagnosis of MR assumptions becomes a growing issue. Although it is not possible to fully prove the validity of MR analyses, the authors used recently developed methods, such as MR-Egger and the weighted median approach, to probe for bias

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due to horizontal pleiotropy (12,13). The authors also conducted sensitivity analyses by excluding genetic variants associated with BMI from the genetic risk scores of the other metabolic traits and divided the genetic risk scores into subsets according to mechanistic pathways to further assess potential horizontal pleiotropy. No evidence of violation was detected in the current study, although some of the statistical tests may have low power to detect particular violation of assumptions. For example, the MR-Egger test can be insensitive to balanced pleiotropy; that is, some variants have positive direct effects while others have negative direct effects (12). Furthermore, MR methods do not allow identification of specific genetic variants with pleiotropic effects that could be excluded from subsequent analysis to strengthen the MR approach. Future MR studies using raw data could further investigate the potential violation of MR assumptions, and additional method development in this relatively new field could increase the sensitivity and power of detecting assumption violation.

The authors did not find evidence of a causal association for type II diabetes and risk of pancreatic cancer, which contradicts the current epidemiological thinking. Recent large meta- or pooled analyses of prospective epidemiological studies have found statistically significantly increased risks that range from 1.4- to approximately two-fold (14,15). Large between-study heterogeneity was observed, which could not be explained when age, sex, smoking, or obesity were considered. Large heterogeneity may reflect either genuine diversity or some form of bias. Type II diabetes begins with insulin resistance and relative hyperinsulinemia, but later in the natural history there is substantial loss of the islet b-cells resulting in hypo-insulinemia. Accordingly, if pancreatic cancer is positively associated with fasting insulin as shown by Carreras-Torres and colleagues (1), the hypo-insulinemia may mask the effect of early type II diabetes on pancreatic cancer. The relationship between diabetes and pancreatic cancer risk is further complicated by the potential for pancreatic cancer to cause diabetes, leading to reverse causation bias, but most epidemiological studies still observed statistically significant associations after excluding participants diagnosed with diabetes within a couple of years of cancer diagnosis. However, a recent critical appraisal of the prospective epidemiological literature on type II diabetes and pancreatic cancer suggested the existence of biases (10), in agreement with the results of the current MR study. Future large pooling consortia of prospective studies and MR investigations should further address these issues.

In summary, Carreras-Torres et al. present evidence for a potential causal role of BMI and fasting insulin in pancreatic cancer risk. However, further work is needed to replicate findings and to reach firmer conclusions.

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