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Understanding the contribution of insulin resistance to the risk of pancreatic cancer

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In the United States, pancreatic adenocarcinoma is the tenth most common cancer diagnosis; however, it is the third most common cause of death due to cancer. Recent estimates suggest that in less than a decade, pancreatic cancer will become the second most common cause of cancer death in the US. The overall 5-year survival rate is only ~10% and has only marginally improved over the past five decades[1].

Though the relationship between diabetes mellitus and pancreatic cancer has been known for over 175 years[2], it remains to be fully understood. The complex relationship between the two diseases has been the subject of numerous clinical, epidemiological, laboratory, and experimental studies. The relationship is bi-directional. While there is strong clinical, epidemiological, and experimental evidence to show that pancreatic cancer causes diabetes mellitus and worsens hyperglycemia[3], there is also evidence that type 2 diabetes is a risk factor for developing pancreatic cancer. In meta-analyses of multiple cohort and case-control studies, type 2 diabetes of >5 years duration has been shown to be a modest risk factor (risk estimates between 1.5–2 fold) for the development of pancreatic cancer[4, 5].

Although type 2 diabetes has been well established as a risk factor for pancreatic cancer, the biological mechanisms that mediate this epidemiological association have not been clearly elucidated. The metabolic disturbances in type 2 diabetes include not only hyperglycemia but also obesity, insulin resistance and compensatory hyperinsulinemia; any or all of which could contribute to the increased risk of pancreatic cancer. Because obesity and insulin resistance are often present in type 2 diabetes, it can be difficult to untangle the independent contributions of the individual components to pancreatic cancer risk. However, the notion that insulin resistance and hyperinsulinemia could contribute to cancer risk is supported by experimental evidence from basic research. Insulin promotes cellular replication via binding

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to the insulin and IGF-1 receptors and activation of the MAPK pathway, which does not share the same resistance to insulin action as the glucose metabolism pathways[6–8].

Insulin resistance can be caused by obesity and precedes the development of type 2 diabetes for years. It is estimated that approximately 42.4% of the US population is obese[9] and 34.5% have pre-diabetes[10]. Therefore, an important area of ongoing research is whether insulin resistance also confers a risk of pancreatic cancer in *non-diabetic* individuals with insulin resistance. This question remains unsettled. A nested case-control study using five large prospective cohorts of non-diabetic US patients previously found an association between hyperinsulinemia and pancreatic cancer risk[11], but markers of insulin resistance were not measured and subjects were predominantly female and of European descent, thus limiting generalization of its findings. More studies are needed in this area, and the study by Kim et al in this issue[12] provides valuable new information on the relationship between insulin resistance and pancreatic cancer mortality.

The authors performed a careful analysis of the relationship between fasting blood glucose, hemoglobin A1c, and surrogate markers of insulin resistance (HOMA-IR and fasting insulin) with pancreatic cancer mortality (used as a surrogate for incidence)[12]. They studied a large observational cohort of over 550,000 Koreans, consisting predominantly of employees of companies or government organizations and their spouses, followed for a median of 8.4 years. The vast majority did not have diabetes, although a small subset was diagnosed with it during screening or had previously diagnosed diabetes. The analyses controlled for potential known confounders and used wash-out periods of up to 5 years into follow-up to exclude potential reverse causality. The authors report a trend for an increase in pancreatic cancer mortality with increasing levels of fasting blood glucose and hemoglobin A1c, and with the presence of insulin resistance and hyperinsulinemia. However, what is particularly noteworthy in their findings was that both HOMA-IR and hyperinsulinemia were risk factors for pancreatic cancer mortality even among subjects without diabetes, demonstrating that insulin resistance is independently associated with increased cancer risk and does not require the presence of hyperglycemic levels observed in type 2 diabetes.

Both the finding and strength of the association between diabetes (screen-detected or previously diagnosed) and pancreatic cancer mortality in the study by Kim et al[12] are similar to previous studies[4, 5], which demonstrates reproducibility and increases confidence in their observations. In addition, the significant associations between pancreatic cancer mortality and prediabetes, insulin resistance, and hyperinsulinemia in nondiabetics are notable. Understanding the impact of a risk factor on disease burden in the population is of great importance as it helps inform public health policy. Because of the low competing mortality from other causes by virtue of being a relatively young cohort, the study of Kim et al provides an opportunity to derive estimates of attributable risk from data presented in tables 2 and 3 of their manuscript[12]. Our calculations yielded attributable risk estimates of 10–13% for prediabetes, 41–47% for screen-detected or previously diagnosed diabetes depending on the definition, i.e. fasting blood sugar or hemoglobin A1c. The corresponding estimate for insulin resistance in the nondiabetic population was 33%. On the other hand, it is important to note that several notable characteristics of their cohort (e.g. younger age, lower body mass index, lower prevalence of diabetes, etc.) make it difficult to generalize these estimates to

populations with different characteristics, especially Western populations. The younger age of the study population probably led to a relatively low pancreatic cancer-related mortality and therefore a longer observation period would be helpful to better determine the impact of diabetes-related morbidity and other competing risks on mortality, including pancreatic cancer.

The findings of this study bring to light yet another reason to address the growing list of comorbidities related to prediabetes and insulin resistance in the general population. Further research is needed to confirm the findings from Kim et al in other populations and to understand the mechanistic basis of the association between insulin resistance with pancreatic cancer.

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