Published in final edited form as:

Clin Cancer Res. 2010 September 1; 16(17): 4313–4318. doi:10.1158/1078-0432.CCR-09-1942.

New Strategies in Pancreatic Cancer: Emerging Epidemiological and Therapeutic Concepts

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Abstract

Pancreatic cancer (PC) is a highly lethal disease with complex etiology involving both environmental and genetic factors. While cigarette smoking is known to explain 25% of cases, data from recent studies suggest that obesity and long-term type II diabetes are two major modifiable risk factors for PC. Furthermore, obesity and diabetes appear to affect the clinical outcome of patients with PC. Understanding the mechanistic effects of obesity and diabetes on the pancreas may identify new strategies for prevention or therapy. Experimental and epidemiological evidence suggests that the antidiabetic drug metformin has protective antitumor activity in PC. In addition to insulin resistance and inflammation as mechanisms of carcinogenesis, obesity and diabetes are linked to impairments in endothelial function and coagulation status, which increase the risks of thrombosis and angiogenesis and in turn the risk of PC development and progression. The associations of the *ABO* blood group gene and *NR5A2* gene variants with PC discovered by recent genome-wide association studies may link insulin resistance, inflammation, and thrombosis to pancreatic carcinogenesis. These exciting findings open new avenues for understanding the etiology of PC and provide opportunities for developing novel strategies for prevention and treatment of this disease.

Keywords

Pancreatic cancer; etiology; epidemiology; therapy

BACKGROUND

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death for both men and women in the U.S. It is one of the most lethal malignancies, with a 5-year survival rate of <5% and median survival duration of less than 6 months (1). According to the American Cancer Society, a total of 42,470 new cases and 35,270 deaths occurred in 2009. Worldwide, PC contributes to more than 230,000 deaths annually.

Cigarette smoking is the most consistently established risk factor for PC, contributing to 25% of cases. Other suspected risk factors include heavy alcohol consumption, chronic pancreatitis, and dietary/endocrine factors (2). As the prevalence of cigarette smoking decreases, and that of obesity and diabetes increases, the latter two are poised to become the major modifiable risk factors for PC in Western countries.

Obesity and Diabetes as Risk Factors for PC

Data on the association of obesity and PC were inconsistent in earlier studies, partially because of improper study design or small sample size. Several recent cohort and case-control studies have reported elevated risks of PC in obese individuals, compared with individuals of normal weight, with relative risks (RR) or odds ratios ranging from 1.2 to 3.0 (3). A recent meta-analysis of 21 independent prospective studies involving 3,495,981 individuals and 8,062 PC patients showed that the RR of PC per 5 kg/m² increase in body mass index (BMI) was 1.16 (95% confidence interval [CI]: 1.06–1.17) in men and 1.10 (95% CI: 1.02–1.19) in women (4). It has been estimated that the population-attributable fraction of obesity-associated PC is 26.9% for the U.S. population (3).

Our recent study in 740 PC cases and 769 cancer-free controls found that overweight (BMI 25–29.9 kg/m²) at ages from 14–19 years to the 30s and obesity (BMI >30 kg/m²) at ages from the 20s to the 40s were significantly associated with increased risk of PC, independent of diabetes (5). The risk leveled off for weight changes after age 40. The stronger association of the disease with weight gain in earlier adulthood than in later adulthood might be explained by the longer duration of exposure to cumulative excessive body fat in the earlier gainers. Because very few individuals overweight or obese at a younger age returned to a normal weight later in life, it is unknown whether the risk of PC could be reduced by successful weight control in middle age. Thus, weight control at younger ages should be one of the primary strategies for the prevention of PC.

Because diabetes is a manifestation of PC, a long-standing controversy exists over the role of type II diabetes in the etiology of this cancer. Examining the duration of diabetes prior to cancer was critical to understanding whether diabetes is a risk factor, in addition to being a consequence, of PC. A meta-analysis of 20 studies published in 1995 estimated that long-standing diabetes (5 years or more) increased PC risk 2-fold (RR, 2.0; 95% CI: 1.2–3.2) (6). In an updated meta-analysis based on 36 studies, the association between established diabetes and PC was slightly weaker than in the earlier meta-analysis but remained statistically significant (RR, 1.5; 95% CI: 1.3–1.8, and RR, 1.5; 95% CI: 1.2–2.0, for groups with 5–9 years or 10+ years of existing diabetes prior to cancer, respectively, compared to nondiabetic individuals) (7). When analyzed separately, results from cohort and case-control studies were similar (7), suggesting that bias is unlikely to explain the excess risk observed in these studies.

The direct relation between blood glucose levels and PC risk has been examined in prospective studies. Both fasting and postload serum glucose levels were significantly associated with increased risk of death from PC (8,9). Results from these studies strongly support a causal role of type II diabetes in PC.

Obesity, Diabetes, and Clinical Outcome of PC

Our recent study found that obesity within a year of PC diagnosis was significantly associated with an average of 5 months shorter overall survival regardless of disease stage and tumor resection status (5). Several other clinical studies have also shown that patients with a higher BMI had worse clinical outcomes than those who had normal BMI (10–12). Although obesity is a risk factor for diabetes, the impact of obesity on PC survival was independent of diabetes (13).

These observations raise questions regarding the mechanisms that underlie the association between obesity and reduced patient survival. There are several possibilities through which obesity could contribute to a worse prognosis: 1) increased risk of diabetes, thrombosis, and other comorbid conditions; 2) impaired immune function and a more aggressive tumor type; and 3) poor response to therapy. Few studies have investigated these issues, and some of the

observations that examined the association between diabetes and PC survival were inconsistent, depending on the populations studied. In general, it has been possible to show that diabetes had a negative effect on survival in patients with resected pancreatic tumors (14,15) but not in patients with late-stage disease (16–18). A recent large meta-analysis found no association between long-term diabetes and survival in PC (19). Further research on the mechanisms of reduced PC survival in obese patients is required, and such efforts may lead to novel therapeutic targets.

ON THE HORIZON

Insulin-like Growth Factor

A recent study in an animal model of PC has shown that the same human PC cell line manifested dramatically different growth patterns in obese mice and in wild-type lean mice (20). In obese mice, tumors grew larger and faster, metastasized more frequently, and caused significantly greater mortality than tumors in lean animals. Rapid tumor growth was not a function of decreased apoptosis, but was related directly to increased cellular proliferation. Interestingly, tumor cell proliferation correlated negatively with the adipokine adiponectin and positively with serum insulin concentration. These observations provided evidence for the direct influence of obesity on PC growth and dissemination and suggested a role for insulin and adipokines in the process.

In obesity, the adipose tissue acts as an endocrine organ, regulating the release of free fatty acids, cytokines, and hormones. The complex interplay of these and other substances leads to insulin resistance and compensatory chronic hyperinsulinemia. Conceptually, the increased level of insulin and consequent higher levels of insulin-like growth factors (IGF) and other proinflammatory cytokines promote cell proliferation, inhibit apoptosis, and enhance angiogenesis, which lead to accelerated tumor development and progression (Fig. 1). Insulin and IGF-1 stimulate the mTOR pathway by activating the insulin receptor substrate-1 and the phosphatidylinositol-3-kinase/Akt signaling pathway (21). Insulin and IGF-1 signaling also integrates with the epidermal growth factor (EGF)/EGF receptor (22), c-Jun-NH2-kinase, and met proto-oncogene signaling pathways (23). Early experience with IGF-1 receptor blockade suggests that the IGF-1 signaling pathway may be an important therapeutic approach for PC. (24)

Nuclear Receptor 5A2

A recent genome-wide association study identified the nuclear receptor 5A2 (*NR5A2*) gene as a significant predisposing factor for PC (25). *NR5A2* belongs to the nuclear hormone receptor superfamily, and is expressed mainly in the liver, intestine, exocrine pancreas, and ovary (26). It plays a crucial role in cholesterol metabolism and steroidogenesis. *NR5A2* has been associated with colon and breast cancers through its functional interaction with the β -catenin/Tcf4 signaling pathway and its stimulation of the estrogen metabolic genes (27). In the pancreas, *NR5A2* is a major downstream component of the pancreatic-duodenal homeobox 1 (*PDX-1*) regulatory complex governing pancreatic development, differentiation, and function (28). *NR5A2* and *PDX-1* are co-expressed in the pancreas during mouse embryonic development, but later *NR5A2* expression becomes restricted to the murine exocrine pancreas (no human data are available). *It has been suggested that NR5A2 is a component of a transcriptional network involving PDX-1 and hepatocyte nuclear factors HNF-1 α , HNF-4 α , and HNF-3 β that regulates pancreatic development and may also play a role in pancreas homeostasis in the adult. Since several transcription factors either upstream or downstream of NR5A2 have been associated with development of diabetes (29), it has been speculated that NR5A2 contributes to diseases linked to pancreatic dysfunction, such as diabetes. Interestingly, the adiponectin gene promoter contains a NR5A2 response element, and NR5A2 plays an*

important role in transcriptional activation of the adiponectin gene (30). Adiponectin is an adipocyte-secreted hormone that has been proposed to be a biological link between obesity (especially central obesity) and increased risk of cancer (31), including PC (32). An *NR5A2* gene variant has been associated with excess BMI in another genome-wide association study (33). Understanding the mechanism through which *NR5A2* contributes to PC, especially obesity- or diabetes-associated PC, may identify novel targets for prevention and treatment.

Obesity, ABO, and Thrombosis

Obesity is a known risk factor for thrombosis. Thrombosis is a frequent complication of PC, with reported incidences ranging from 17% to 57% (34). Thromboembolic events usually are related to poor prognosis in patients with cancer. Other general risk factors for thrombosis in malignancy include retroperitoneal tumor location, decreased activity in bedridden patients, frequent hospitalizations, radiation injury to blood vessels, and hypercoagulability. Patients with PC are often in a hypercoagulable state with increased plasma levels of pro-coagulants, such as tissue factor, thrombin, and fibrinogen, and decreased levels of coagulation inhibitors, such as antithrombin III, heparin cofactor II, protein C, free protein S, and thrombomodulin (35). The hypercoagulable state can promote angiogenesis, inflammation, and development of metastasis. The potential mechanisms that link obesity and thrombosis with poor prognosis in PC include insulin resistance, inflammation, and hypercoagulability (36).

Physiologic insulin levels can activate the nitric oxide pathway in endothelial cells, which has beneficial antiatherogenic effects through nitric oxide-mediated vasodilation. Under insulin resistance conditions, however, the mitogenic and atherogenic pathways of insulin action signaling through the *ras* pathway (37) may lead to thrombosis via increased production of plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor (VEGF) and synthesis and degradation of extracellular matrix proteins (36). Previous studies have shown that obese mice had significantly higher plasma levels of coagulation factors such as PAI-1 and antithrombin III antigen, and greater factor VIII activity and combined factor II/VII/IX activity than lean mice (38). In women, a positive relationship between BMI and plasma concentrations of coagulation factors and PAI-1 has also been reported (39). Besides PAI-1 excess, other physiologic changes characterizing obesity, such as endothelial cell dysfunction and increased platelet aggregation, could also contribute to thrombosis (40).

The genome-wide association study finding that the *ABO* blood gene was associated with PC (41) and the phenotypic finding in a large cohort study that individuals with the non-O blood types had a higher risk of PC (42) suggest that the ABO system has an important role in human cancer. Mechanistically, ABO may contribute to PC through inflammation (41) and thrombosis (43,44). The *ABO* gene codes for several glycosyl transferases that add sugar residues to the H(O) antigen, thus forming the A and B antigens. These antigens reside on the surface of von Willebrand factor (VWF), a carrier protein for coagulation factor VIII. The clearance of VWF has been associated with the ABO antigen type (45). Individuals with the *ABO* A1 and B alleles have higher plasma levels of VWF and factor VIII (46), which confer a higher risk of thrombosis.

Few studies have addressed the relationship between obesity or ABO and thrombosis in PC. Better understanding the association between hypercoagulability and PC may provide new insights on the tumor biology and management of the disease to improve patient survival.

Metformin as a Potential Chemopreventive and Therapeutic Agent

Except avoiding cigarette smoking and maintaining a healthy lifestyle, no known method or chemopreventive agent has been demonstrated to reduce the risk of PC among individuals at higher than normal risk for the disease. Recent findings from both epidemiological

investigations and experimental systems suggest that metformin, a hypoglycemic agent used in the management of diabetes, may be a potential chemopreventive agent for PC.

Two epidemiological investigations in patients with type II diabetes found that the patients taking metformin had a reduced risk of cancer. These results were significant both before and after adjusting for BMI (47,48). In the first study, metformin use among 11,876 diabetic patients, including 923 cancer cases, was associated with a 21% reduced risk for all types of malignancies, and a dose-response relationship was observed. In the second study, 2,109 of 62,809 diabetic patients developed cancer. Compared to patients treated with metformin monotherapy, those treated with sulfonylurea and insulin had 1.36- and 1.42-fold higher risks of cancer, respectively. The antidiabetic therapy-associated variation in cancer risk was not seen in patients with breast or prostate cancer but was documented in patients with colorectal cancer or PC. Our recent study in 973 patients with PC (including 259 with diabetes) and 863 controls (109 with diabetes) has shown that treatment with metformin was associated with a 62% reduction in risk of PC (49). Although the choice of antidiabetic therapy could be related to the severity of diabetes, and that could confound the association between antidiabetic therapy and risk of cancer, the validity of these observations is supported by a large amount of experimental evidence of the antitumor activity of metformin.

Metformin is a glucose-lowering drug of the biguanide class that also has a weight-reducing effect (50). Metformin decreases, rather than increases, fasting plasma insulin concentrations and acts by enhancing insulin sensitivity via activation of γ -AMP-activated protein kinase (AMPK). Apart from its important hormonal metabolic effects, metformin can inhibit proliferation and stimulate apoptosis in tumor cell lines (50) as well as in experimental animals (52). A study in a hamster model of PC showed metformin to have a significant protective effect on pancreatic tumor development induced by a chemical carcinogen and high-fat diet (53). Metformin has been shown to disrupt crosstalk between insulin and G protein-coupled receptor signaling systems through its agonistic effect on AMPK in human PC cells and to inhibit growth of human PC cells xenografted into nude mice (54). Metformin also was found to enhance immune cell (T cell) memory by altering cellular metabolism (55,56), and in patients with type II diabetes, metformin treatment was associated with biochemical evidence of improvement of endothelial function, including decreased plasma levels of VWF, soluble vascular cell adhesion molecule-1, soluble E-selectin, tissue-type plasminogen activator, PAI-1, and VEGF (57–60). Dysfunction of the vascular endothelium and elevated levels of these circulating proteins may play important roles in tumor development and progression via induction of thrombosis and angiogenesis. Interestingly, a recent retrospective study of 2,529 breast cancer patients who received chemotherapy for early stage disease found that the patients with diabetes (n=68) who received metformin had a 3 times higher pathologic complete response rate than diabetic patients not receiving metformin (n=87) (61). These experimental observations provide a strong biological rationale for investigating metformin as an antitumor and chemopreventive agent. The efficacy of metformin as an adjuvant therapy for breast cancer is being tested in clinical trials. Whether metformin or other AMPK agonists have therapeutic value in the prevention or treatment of PC should be further examined in the laboratory and in prospective clinical trials.

Summary

Obesity and diabetes play important and increasingly well-understood roles in the development and progression of PC through mechanisms mediated by insulin resistance, inflammation, and hypercoagulability. The recent genome-wide association study findings implicating the *NR5A2* and *ABO* genes in PC support this hypothesis. Emerging from these genetic and molecular epidemiologic data is evidence that metformin and other AMPK agonists may have useful chemopreventive or therapeutic effects in PC. Further research to explore the links

between genetic and molecular epidemiology and pancreatic carcinogenesis will lead to a better understanding of the etiology of PC and development of novel strategies for prevention and treatment of this challenging disease.

Acknowledgments

Supported in part by 5 P20 CA101936 SPORE in Pancreatic Cancer (Abbruzzese) and RO1 CA98380 (Li).

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Fig. 1.
Contributions of obesity and diabetes to the development and progression of pancreatic cancer.