Review Article

Glucose intolerance and the risk of pancreatic cancer

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Abstract: Mortality due to pancreatic cancer is increasing globally in most industrialized countries including Japan. The prognosis of pancreatic cancer is still extremely poor, despite various advances in diagnostic imaging techniques and medical treatment, and the 5-year survival rate remains less than 10%. Early detection of pancreatic cancer is essential for improving outcome, and identifying patients who at high risk is a major concern. Several reported factors can increase the risk of acquiring the genetic mutations that may potentially result in pancreatic cancer. Diabetes has the highest incidence among diseases that may be complicated by pancreatic cancer. In clinical practice, many cases of pancreatic cancer are diagnosed as a result of studies of worsening glycemic control. Glucose intolerance is a pre-diabetic state of hyperglycemia associated with insulin resistance and increased risk of both future diabetes and adverse outcomes. In the future, for early detection and treatment of pancreatic cancer, we believe that it is critical to share consensus with diabetologists, and to perform adequate screening for pancreatic cancer in patients with glucose intolerance.

Keywords: Pancreatic cancer; diabetes; hyperglycemia; insulin resistance

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Introduction

Mortality due to pancreatic cancer is increasing globally in most industrialized countries including Japan, with an estimated 227,000 deaths per year worldwide (1). According to the national statistics of 2011 in Japan, there were 28,829 deaths due to pancreatic cancer, ranking it fifth after lung cancer, gastric cancer, colorectal cancer, and liver cancer (2-4). The prognosis of pancreatic cancer is still extremely poor despite advances in various diagnostic imaging techniques and medical treatment, with a 5-year survival rate of less than 10% (5,6). Early-stage pancreatic cancer is usually clinically silent, and the disease only becomes apparent after the tumor invades into surrounding tissues or metastasizes to distant organs. Early detection of pancreatic cancer is required for improving the outcome, and recognition of high-risk patients is a major issue.

Risk factors for pancreatic cancer

Certain factors can increase the risk of acquiring the genetic mutations that may potentially result in pancreatic cancer (*Table 1*). Risk factors for this malignant disease include cigarette smoking (14-17), family history (7,8,18-21), advancing age, male sex, diabetes mellitus, chronic pancreatitis (12), hereditary pancreatitis (13), obesity (11,22-27), non-O blood group (28,29), a high-fat diet, diets high in meat and low in vegetables, and folate deficiency (1).

Cigarette smoking is one of the biggest risk factors for the development of pancreatic cancer. Heavy smokers have a 2-3-fold increased risk of death due to pancreatic cancer compared with non-smokers.

A family history of pancreatic cancer is also an important risk factor (7,8,18-21); about 3-9% of pancreatic cancer patients have such a family history. Ghadirian *et al*., found that 7.8% of all patients with pancreatic cancer and only 0.6% of controls had a family history of pancreatic cancer, i.e., a 13-fold difference, with no differences in environmental risk factors between the two groups (18). In a meta-analysis of familial risks in pancreatic cancer, Permuth-Wey *et al*. concluded that results from case-

Table 1 Risk factors of pancreatic cancer

Risk factors	Items	Risk	References
Family history	Pancreatic cancer	1.8-13 fold	(1,7)
	Genetic syndromes	2-132 fold	(8)
Complication	Diabetes mellitus	1.8-2.1 fold	(9,10)
	Obesity	3.5 fold	(11)
	Chronic pancreatitis	4-8 fold	(12)
	Hereditary pancreatitis	53 fold	(13)
Favorite item	Cigarette smoking	2-3 fold	(14-17)

Among the risk factors for pancreatic cancer, the ratio is high for those mentioned in the columns.

control [RR =2.82; 95% confidence interval (CI): 1.99-3.66] and cohort (RR =1.62; 95% CI: 1.28-1.97) studies showed a significant increase in pancreatic cancer risk if a relative had been affected, with an overall summary RR =1.80 (95% CI: 1.48-2.12) (8). Familial pancreatic cancer has been defined in most studies as the presence of pancreatic tumors in a pair of first-degree relatives. Prospective analysis of families with this malignant disease shows that first-degree relatives of individuals with familial pancreatic cancer have a 9-fold increased risk of this neoplasm over the general population (18). This risk rises to 32-fold in kindred with three or more first-degree relatives with pancreatic cancer.

Diabetes is a very important risk factor for disease, as described in detail later.

Obesity and being overweight increase the risk of pancreatic cancer significantly. According to a large-scale cohort study performed in Japan (11), men with a BMI of 30 kg/m^2 or more at age 20 years had a 3.5-fold higher risk than men with a normal BMI. Women with a BMI of 27.5-29.9 at the baseline had a ~60% increased risk compared with women with a BMI of 20.0-22.4. In men, weight loss of 5 kg or more between 20 years of age and the baseline age was associated with an increased risk of pancreatic cancer death.

On the other hand, no correlation has been observed between pancreatic cancer and BMI in two other cohort studies (22,23). One report has indicated that the estimated summary RR of pancreatic cancer per 5 kg/m^2 increase in BMI was 1.12 (95% CI: 1.06-1.17) in men and women combined (24). Compared with those with a BMI of 18.5-<25, individuals with a BMI of ≥35 had a 45% greater pancreatic cancer risk (95% CI: 1.04-2.02) (25). Being overweight or obese during early adulthood is associated with a greater risk of pancreatic cancer and a younger age at disease onset (26).

Complex relationship between diabetes and pancreatic cancer

Glucose intolerance is a pre-diabetic state of hyperglycemia associated with insulin resistance and increased risk of future diabetes and adverse outcomes. According to the criteria of the World Health Organization and the American Diabetes Association, glucose intolerance is defined as a two-hour glucose level of 140-199 mg/dL in the 75-gram oral glucose tolerance test.

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar levels. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes, and this leads to serious damage to many body's systems over time, especially the nerves and blood vessels. The classification of glucose metabolism disorders is principally derived from etiology, and includes staging of pathophysiology based on the degree of deficiency of insulin action. These disorders are classified into four groups: (I) type 1 diabetes mellitus; (II) type 2 diabetes mellitus; (III) diabetes mellitus due to other specific mechanisms or diseases; and (IV) gestational diabetes mellitus. Type 1 diabetes is characterized by destruction of pancreatic β-cells. Type 2 diabetes is characterized by combinations of decreased insulin secretion and decreased insulin sensitivity (insulin resistance) (30).

In medical practice, many cases of pancreatic cancer are diagnosed as a result of worsening glycemic control. Diabetes has the highest incidence among diseases that are complicated by pancreatic cancer, with a rate as high as 25.9% according to the pancreatic cancer registry report of 2007 (Committee for Pancreatic Cancer Registry, Japan Pancreas Society) (31). There have been many arguments regarding whether or not diabetes is the cause or result of pancreatic cancer (9,10,32-39); however, details of the molecular biologic mechanism itself have not yet been clarified. Understanding the effect of the pathophysiology of diabetes on the pancreatic duct epithelium is believed to be very important for achieving early detection of pancreatic cancer.

In 1994, the Italian Pancreatic Cancer Study Group published a case control study of 720 patients with pancreatic cancer. This study concluded that the increased prevalence of diabetes mellitus in these patients was likely

Table 2 Important studies regarding diabetes and the risk of pancreatic cancer

Reference	Studies	Summary RR (95% CI)
Ben *et al*. [2011]	35 cohort studies	1,94 (1.66-2.27)
Donghui Li *et al*. [2011]	3 case-control studies	1.8 (1.5-2.1)
Huxley R *et al*. [2005]	36 studies	1.82 (1.66-1.89)
Jee SH *et al*. [2005]	Cohort study	1.29 (1.22-1.37)
Gapstu S M *et al*. [2000]	Cohort study	2.15 (1.22-3.80)
Everhart *et al*. [1995]	20 studies	2.1 (1.1-2.7)
Gullo L *et al*. [1994]	Case control study	3.04 (2.21-4.17)

These are representative articles reporting the relationship between diabetes and the risk of pancreatic cancer. There are also strong clinical, epidemiological, and experimental evidences suggesting pancreatic cancer relates to diabetes.

related to the diabetes caused by the tumor (34).

Mizuno *et al*. reported a retrospective study of 540 pancreatic cancer patients that showed that the prevalence of diabetes in different stages of pancreatic cancer was 45%, of which more than half were less than 2 years in duration (35). Their data showed that even though the prognosis of pancreatic cancer patients complicated by diabetes was the same as that of patients without diabetes, outcome and survival were better if they were diagnosed in association with diabetes alone (median survival time: 20.2 months), compared to patients diagnosed on the basis of symptoms such as pain, jaundice, and/or appetite loss (10.2 months, P<0.01).

There is also strong clinical, epidemiological, and experimental evidence that pancreatic cancer causes diabetes (*Table 2*). Hyperglycemia and diabetes mellitus occur in approximately 85% of patients with pancreatic cancer, diabetes being present in 45-67% of patients with pancreatic cancer, depending on how the presence of diabetes is ascertained. The majority (approximately 75%) of diabetes in patients with pancreatic cancer is new-onset (i.e., less than 3 years in duration). New-onset diabetes often resolves when the cancer is resected (36).

Huxley *et al*. performed a meta-analysis of 9,220 cases of pancreatic cancer in 36 reports published between 1966 and 2005 (19 cohort studies and 17 case-control studies). They reported that the relative risk of developing pancreatic cancer in diabetes patients was 1.82 (95% CI: 1.66-1.89) (9). Everhart *et al*., performed a meta-analysis of 20 reports published between 1975 and 1994 (9 cohort studies and 11 case-control studies) of patients suffering from diabetes from one year or more prior to diagnosis of pancreatic cancer in which the relative risk of pancreatic cancer was appropriately calculated. They reported that the relative risk of pancreatic cancer in diabetes patients was 2.1 (95% CI: 1.1-2.7) (10). Moreover, Gapstur *et al*. extracted 35,640 men and women (average age: 40 years) and performed a 25-year prospective study of the relationship between the blood glucose level at one hour in the 50-g oral glucose tolerance test (OGTT) and the onset of pancreatic cancer. They reported that the relative risk of pancreatic cancer was 1.65 (95% CI: 1.05-2.60) in the group with a mild blood glucose increase of 120-159 mg/dL, 1.60 (95% CI: 0.95-2.70) in the group with a glucose level of 160-199 mg/dL, and 2.15 (95% CI: 1.22-3.80) in the group with a glucose level of 200 mg/dL or more compared with control cases in which the blood glucose level at one hour was 119 mg/dL or less. There was a significant relationship between the increase in blood glucose and the onset of pancreatic cancer (37).

The complex relationship between the two diseases has been the subject of numerous clinical, epidemiological, and experimental studies. Epidemiologic studies have suggested that long-standing type 2 diabetes is a modest risk factor for the development of pancreatic cancer. Meta-analysis of multiple cohort and case control studies has shown that the risk of pancreatic cancer in patients who have had diabetes for more than 5 years is 1.5- to 2-fold higher. This is not fully explained by risk factors such as obesity that are shared between the two diseases (38).

Possible mechanism of carcinogenesis in obesity and diabetes

Previous reports have indicated that hyperinsulinemia (40), insulin resistance (41) and insulin-like growth factor (IGF) gene polymorphisms (42) affect the onset of pancreatic cancer.

Insulin analogs and stimulators of insulin secretion used for treatment of diabetes increase the risk of pancreatic cancer, whereas metformin reduces the onset and death rate of pancreatic cancer (43).

It has been reported that a high insulin level promotes the growth of human pancreatic cancer cell lines (44,45),

and that hyperglycemia and a high fatty acid level promote the growth of pancreatic cancer cells (46).

Butler *et al*. classified 45 autopsied samples of pancreas tissue from patients into 4 groups depending on BMI and the presence of type 2 diabetes, then histologically compared and investigated the proliferation of pancreatic duct epithelium using Ki67 immunostaining (47). They found that the Ki67 positivity rate in the pancreatic duct epithelium was significantly (4-fold) higher in the diabetic group with BMI <25 than in the non-diabetic group with BMI <25, while the Ki67 positivity rate was approximately 10-fold higher in the non-diabetic group with BMI >27, and 14.3-fold higher in the diabetic group with BMI >27. These results suggest that the proliferation of pancreatic duct epithelium is accelerated in diabetic and obese patients. Accordingly, it is surmised that hyperglycemia due to diabetes is involved in the accelerated proliferation of pancreatic duct epithelium, and that furthermore, hyperinsulinemia, which is observed in insulin-resistant obese patients, is also involved in the accelerated proliferation of pancreatic duct epithelial cells.

Recent findings from both epidemiologic investigations and experimental systems suggest that metformin, a hypoglycemic agent used in the management of diabetes, may be a potential chemopreventive agent for pancreatic cancer. Two epidemiologic investigations in patients with type II diabetes found that patients taking metformin had a reduced risk of cancer (48,49). These results were significant both before and after adjusting for BMI. Evans *et al*., reported that 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. Currie *et al*., reported that 2,109 of 62,809 diabetic patients developed cancer. Compared with patients treated with metformin monotherapy, those treated with sulfonylurea and insulin had 1.36- and 1.42-fold higher risks of cancer, respectively.

Li *et al*., compared and investigated the treatment regimen of diabetes and the pancreatic carcinogenesis rate, and found that while insulin analog and insulin secretagogue respectively increased the risk of pancreatic cancer onset in diabetic patients by approximately 4.99- and 2.52-fold, metformin, which is an insulin resistance-improving drug that does not increase the insulin concentration in blood, reduced the risk of pancreatic cancer by 62%, and even when metformin treatment was continued for 5 years or longer (50). Metformin is known to have a direct effect on the activation of AMP-activated protein kinase (AMPK), and mediates cell proliferation and apoptosis via p53 and p27kip1. Furthermore, protein synthesis and cell growth are inhibited due to inhibition of the mammalian target of rapamycin (mTOR) (51). Yang *et al*., reported that the molecular mechanism involved in cell proliferation via AMPK and mTOR is involved in the carcinogenesis of pancreatic cancer against a background of diabetes (52). As is evident from these reports, it is believed that various molecular mechanisms are involved in the increased cell proliferation due to hyperglycemia and hyperinsulinemia, and that clarifying these mechanisms will lead to the future prevention and treatment of pancreatic cancer.

In addition, one of the possible mechanisms of carcinogenesis resulting from obesity and diabetes is oxidative stress. In a study of the mechanism of oxidative stress in diabetics, Giardino *et al*. cultured vascular endothelial cells in the presence of a high sugar concentration and found that reactive oxygen species (ROS) did not increase in the culture medium, whereas in the cells oxidative stress increased due to diabetes, rather than an increase in ROS (53). Moreover, Nishikawa *et al*. investigated the involvement of the mitochondrial electron transport system as a source of intracellular ROS production in diabetes, and found that the generation of mitochondria-mediated ROS played a major role in the expression of intracellular metabolic disorder due to high glucose (54). Furthermore, it has been reported that the ROS generated in this manner damage the genomic DNA involved in cell proliferation in various ways, and may be involved in carcinogenesis (55). It is believed that hyperglycemia damages the DNA of pancreatic duct epithelia through oxidative stress, leading to the onset of pancreatic cancer. In this way, it is considered that hyperglycemia and hyperinsulinemia due to diabetes, obesity and glucose intolerance are involved in accelerated cell proliferation in the pancreatic duct epithelium cell. Various molecular mechanisms are involved in carcinogenesis due to hyperglycemia and hyperinsulinemia, and clarification of these mechanisms will lead to methods for prevention and treatment of pancreatic cancer (*Figure 1*).

Conclusions

In the future, for early detection and treatment of pancreatic cancer, we believe that it is critical to share consensus with diabetologists, and perform adequate screening for pancreatic cancer in patients with glucose intolerance. As described above, it is important to consider the relationship

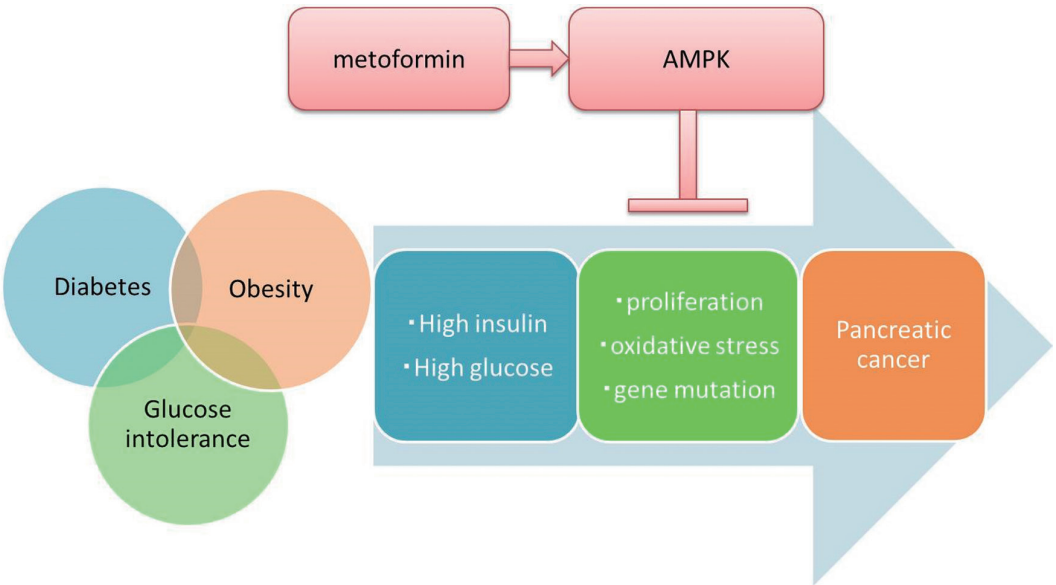

Figure 1 Possible mechanism of carcinogenesis in obesity and diabetes. Hyperglycemia and hyperinsulinemia due to diabetes, obesity and glucose intolerance are believed to be involved in the accelerated proliferation of pancreatic duct epithelial cells. Various molecular mechanisms are involved in carcinogenesis due to hyperglycemia and hyperinsulinemia, and clarification of these mechanisms will lead to methods for prevention and treatment of pancreatic cancer.

of diabetes with pancreatic cancer, and to bear in mind that diabetes is an important factor for early detection of pancreatic cancer. However, pancreatic cancer screening for all diabetes patients is inefficient, because diabetic morbidity is very high. Therefore the determination of specific risk factors and an appropriate time point for screening in diabetes patients is required.

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