

## HIGHLIGHT ARTICLE

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# Diabetes and Pancreatic Cancer

*Highlights from the "2014 ASCO Gastrointestinal Cancers Symposium".  
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### Summary

**Context** Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. Most of the patients are diagnosed in the metastatic staging. Consolidated risk factors include chronic pancreatitis, smoking and family history. Although controversial, diabetes mellitus has been increasingly associated with pancreatic cancer as a risk factor as opposed to just a manifestation of the disease. Biomarkers for early diagnosis of pancreatic cancer among diabetic patients and metformin as a biologic therapy for pancreatic cancer are herein discussed. **Methods** Review of the literature and evaluation of two Abstracts (#180 and #253) from the 2014 ASCO Gastrointestinal Cancers Symposium focusing on pancreatic adenocarcinoma and diabetes diagnosis and therapeutics. **Results** Abstract #180 discusses the role of metabolic biomarkers in the early diagnosis of pancreatic cancer among diabetic patients, especially recently diagnosed. Abstract #253 debates metformin as a candidate radiosensitizer for pancreatic cancer, although it fails to reject its null hypothesis. **Conclusion** Search for methods that can identify pancreatic cancer patients among new-onset diabetic patients could result in early diagnosis of this lethal disease. Metformin is a target therapy that increases median overall survival but is not a radiation sensitizer in patients with pancreatic cancer who present with diabetes.

### Introduction

Pancreatic cancer is an ominous disease, and although it is the 10<sup>th</sup> most prevalent cancer, it is the 4<sup>th</sup> leading cause of cancer mortality, with a 5-year overall survival of only 6%. Up to 45% of the pancreatic cancer cases can present as new-onset diabetes. There is a mounting body of evidence showing that diabetes mellitus is a risk factor for pancreatic cancer [1, 2]. Most of the studies have been finding a relative risk close to 2 of pancreatic cancer in diabetic patients [3, 4]. However, some early studies found that new-onset diabetes has the strongest association with pancreatic cancer and is largely the responsible for the link between diabetes and pancreatic adenocarcinoma. As diabetes could be a manifestation of pancreatic cancer, it has been controversial if diabetes is a real risk factor for pancreatic cancer. Recent cohorts have been favoring diabetes mellitus and even metabolic syndrome as a real risk factor for

pancreatic cancer [5]. It is of paramount importance to define biomarkers among patient with new-onset diabetes who could otherwise have pancreatic cancer. Metformin, on the other hand, has been proven to be more than a mere glucose control drug in the impact on the overall survival of diabetic patients with pancreatic cancer [6]. The molecular underpinnings of metformin in pancreatic cancer are here discussed.

### What We Knew Before the 2014 ASCO Gastroenterology Cancers Symposium

#### Diabetes and Pancreatic Cancer

The Italian Pancreatic Cancer Study Group discovered a three-fold risk of pancreatic malignancy in patients with diabetes (odds ratio: 3.04; 95% CI: 2.21-4.17) [7]. Once they repeated the analysis to include only patients diagnosed with diabetes for more than three years, there was no statistical significance (odds ratio: 1.43; 95% CI: 0.98-2.07). They reported that 40.2% of patients with pancreatic cancer and diabetes were diagnosed concomitantly or 15.9 % were diagnosed within two years prior to the diagnosis of cancer. In men, the risk of pancreatic cancer increased with longer duration of diabetes in a Korean ten-year prospective study investigating serum fasting glucose and its association with malignancy [8]. In a

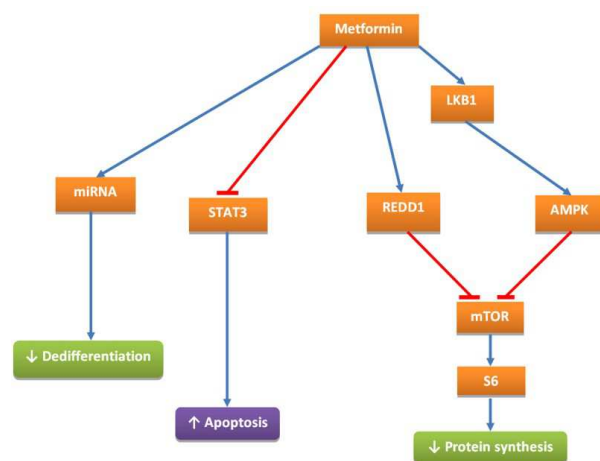
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veterans system study comparing 109,191 diabetic patients with 211,695 non-diabetic patients, 124 patients in the diabetic cohort and 140 in the non-diabetic cohort developed pancreatic cancer, resulting in a hazard ratio of 2.17 (95% CI: 1.70-2.77) [9]. In a Taiwanese cohort that included 39,515 patients followed for 7 years, diabetes mellitus was associated with a relative risk of 2.75% (95% CI: 2.51-3.02) in developing pancreatic cancer and other gastrointestinal tumors [10]. A Johns Hopkins study established HbA1C as a predictor and prognostic factor in pancreatic cancer [11]. New-onset diabetes is associated with worse survival in patients with pancreatic ductal adenocarcinoma who undergo pancreatectomy [12]. Diabetes mellitus is associated with improved overall survival (8.4 months) compared to euglycemic controls (7.5 months; P=0.04) among patients with pancreatic cancer. Recent-onset diabetes survival averaged 9.8 months as opposed to the 7.9 months of survival of diabetes diagnosed 2 years previous to pancreatic cancer diagnosis (HR=0.789, P=0.142) [13].

#### Metformin and Pancreatic Cancer

In a Taiwanese cohort, metformin users had decreased risk of pancreatic malignancy with hazard ratio of 0.15 (95% CI: 0.03-0.79) [14]. A meta-analysis by Zhang *et al.* showed a relative risk of pancreatic cancer of 0.54 among metformin users [15]. In a MD Anderson Cancer Center study following patients with diabetes and pancreatic malignancy from 2000 to 2009, metformin users had a prolonged median survival compared to non-users: 16.6 vs. 11.5 months (P=0.0044) with a 33% decreased risk of death (hazard ratio: 0.67, 95% CI: 0.51-0.88; P=0.005) [16]. A similar benefit was achieved in a study by Esbah *et al.*, when stage 3 pancreatic adenocarcinoma patients with diabetes using metformin had an overall survival of 16 months compared to 10 months among non-users (P=0.02) [17].



**Figure 1.** Metformin effect in cellular pathways involved in pancreatic cancer.

#### **What We Have Learned at the 2014 ASCO Gastrointestinal Cancers Symposium**

##### *Discrete Plasma Biomarkers in Pancreatic Cancer-Associated Diabetes (Abstract #180) [18].*

Urayama *et al.* performed a prospective cohort study to identify biomarkers that could detect pancreatic adenocarcinoma among diabetic patients. Their population was composed of 36 patients with pancreatic adenocarcinoma and diabetes onset within 3 years of the cancer diagnosis and 22 patients with long history of diabetes (more than 3 years since diagnosis) and no pancreatic adenocarcinoma. The accuracy of a set with 15 features (AUC=0.964) promise a future validation in a larger new-onset diabetic population.

##### *Metformin Is not a Radiation Sensitizer in Specific Cell Lines (Abstract #253) [19].*

Dorth *et al.* executed a preclinical study to refute the hypothesis that metformin is not a radiation sensitizer in pancreatic cancer. They cultured a human pancreatic cell line (MiaPaCa-2) in two concentration media with normal and supra-physiologic glucose concentration and incubated for 3-7 days with or without metformin. The resultant clones were exposed to radiation to measure clonogenic survival. After no difference in clonogenic survival was appreciated, this study could not reject its null hypothesis. They also tried to demonstrate that metformin increases AMPK phosphorylation, which inhibit mTOR and cell growth (Figure 1). AMPK is a kinase that senses ATP depleted cellular conditions, which could explain why in this study a physiologic glucose medium depleted by a cell with ongoing metabolic needs but not a supra-physiologic glucose medium had increased AMPK phosphorylation.

#### **Commentary**

Identification of biomarkers for early diagnosis of pancreatic cancer is a hot topic of investigation as around 60% of these patients present with metastatic disease. Identifying who among new-onset diabetes patients would be also a pancreatic cancer patient is no small task. In the prospective study abovementioned, a population with new-onset diabetes and pancreatic adenocarcinoma was compared to a heterogeneous long-standing diabetic population that was considered as not having pancreatic adenocarcinoma. Furthermore, as the biomarkers were supposed to discriminate pancreatic cancer in a defined population (diagnosis within probably 5 years as pancreatic cancer has a poor overall survival), their control should be a recently diagnosed group of patients with diabetes, as the underlying epigenetic, proteomic and metabolomic milieu would certainly be altered by the duration of the disease.

Metformin was found to be a mTOR inhibitor and this knowledge led to a search for targeted therapy especially in pancreatic cancer associated with new-onset diabetes. The inhibition of the mTOR pathway leads to cell cycle arrest; thus, maybe counter-regulatory mechanisms, such as DNA damage response and cell-cycle checkpoints that act against radiation and DNA targeting therapies, are enhanced under metformin influence and were responsible for the neutral results in the radiation sensitization study. Moreover, the study presented here [19] has chosen a specific cell line to generalize that metformin is not a radiation sensitizer in pancreatic cancer.

Metabolomics, proteomics and epigenetics have been trying to apply their methods in order to recognize early biomarkers of parenchymal cells from pancreatic cancer in a scenario where most of the patients are in the metastatic staging on presentation. The chance of success will depend on even more sensitive screening methods and on increasingly precise roadmaps of the cancer metabolomics. It is a necessary step but still far considering that The Cancer Genome Atlas (<http://cancergenome.nih.gov>) is in its inception. Also, the tumor microenvironment could afford more available tumor biomarkers and target of therapies, as stromal cells can compose up to 90% of the mass of pancreatic adenocarcinoma [20].

It is noteworthy to consider that metformin, a widespread medication, can add 4 to 6 months to the median overall survival of a population with a reserved prognosis cancer such as pancreatic adenocarcinoma. In comparison, established target therapies such as bevacizumab in lung cancer add only 2 months to the overall survival of non-small cell lung cancer. Also, it would be interesting to study how metformin interferes in cell-cycle arrest, senescence and apoptosis of malignant cells of a plethora of other adenocarcinomas, as the mTOR pathway is a catalyzer of these cellular processes.

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**Conflict of interest** The authors have no potential conflict of interest

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