

HIGHLIGHT ARTICLE

Risk Determination for Pancreatic Cancer

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ABSTRACT

Pancreatic cancer represents one of the leading causes of cancer related deaths worldwide and constitutes a major public health problem. Despite the advances in diagnosis and treatment, the overall five-year survival remains low, thus leading the focus of medical research towards the identification and modification of potential risk factors. This year, in ASCO Annual Meeting two interesting studies were presented. Ghani et al. (abstract #e15183) sought to investigate the effect of smoking on chemotherapy response in patients with metastatic pancreatic cancer, while Walker et al. (abstract #4117) presented the results of their study regarding the effect of statin use in the prevention of pancreatic cancer. Both studies concluded to useful results that along with the existing literature may further stimulate medical research towards better recognition of risk factors and the application of this knowledge in the clinical practice.

Introduction

Pancreatic cancer is the 13th most common type of cancer worldwide and the fourth leading cause of cancer-related mortality in the United States [1]. Approximately 45,220 people were diagnosed with pancreatic adenocarcinoma and 38,460 died from it in 2013 [2]. Despite the ongoing advances in diagnosis and treatment of pancreatic cancer, the overall five-year survival rate from all stages of the disease remains as low as 5% [3]. Therefore, the determination and modification of potential risk factors, is imperative in the effort to improve the outcomes of this disease.

What We Knew Before 2014 ASCO Annual Meeting?

Numerous, putative risk factors have been identified and associated with the development of pancreatic carcinoma. These factors are summarized in Table 1. Smoking has been found to play a predominant role among them, although the increase in risk is relatively small [4-6]. Importantly, smoke cessation can reduce the conferred risk. It has been reported that the risk of developing cancer after cessation

of tobacco use for 5 year, is comparable to the risk of a never-smoker [6].

Apart from the identification of risk factors that are associated with the development of pancreatic cancer, it is of great importance to also recognize factors that can reduce this risk. To this direction, the use of agents that reduce plasma cholesterol, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, has shown encouraging results in chemoprevention of pancreatic cancer [7]. However, several epidemiological studies have evaluated the relationship between the use of statins and the risk to develop pancreatic cancer with ambiguous findings [8-12].

What We Learnt At 2014 ASCO Annual Meeting?

The Impact of Cigarette Smoking On Treatment Outcome in Metastatic Pancreatic Cancer Patients

Smoking has been identified as one of the main risk factors that contribute in the development of pancreatic cancer [4-6]. However, the association between tobacco use and survival of patients with metastatic pancreatic cancer remains unclear. This topic was the subject of an abstract presented by Ghani et al. [13]. The authors conducted a retrospective study including 445 patients managed in their institution during a 13-year period. The patients were allocated into 2 groups, namely "current smokers" and "non-smokers" based on their tobacco use habits and the overall survival was analyzed.

The presented results showed a trend towards decreased overall survival in "current smokers" who received chemotherapy (p=0.069). This adverse outcome seemed to be more pronounced in male patients, under the age of 60, but this correlation was not statistically significant

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Table 1. Risk factors implicated in the development for pancreatic carcinoma.

Risk Factors For Pancreatic Cancer
Tobacco smoking
• Carbon monoxide, nicotine, cyanide, ammonia, benzene, nitrosamines, vinyl chloride
Occupational factors
• Chlorinated hydrocarbon solvents, nickel compounds, chromium compounds, polycyclic aromatic hydrocarbons, organochlorine insecticides, aliphatic solvents, silica dust
Demographic factors
• Older age, African American race, Ashkenazic Jewish race
Host factors
• Diabetes mellitus, chronic liver cirrhosis, pancreatitis, high-cholesterol diet, consumption of red/processed meat and dietary products, obesity, prior cholecystectomy
Infectious diseases
• Helicobacter pylori infection, hepatitis B virus infection
Genetic predisposition
• Mutations: K-ras, p53, DPC4, p16, BRCA2, MLH1, FANC-G, PALB2
• Inherited syndromes: hereditary pancreatitis, Peutz-Jeghers, Ataxia-telangiectasia, Familial atypical multiple mole melanoma, nonpolyposis colorectal cancer (Lynch II type), hereditary breast and ovarian cancer

($p=0.06$). Additionally the authors found that the survival of patients who received chemotherapy was superior to those who did not. These results suggest a potential adverse implication of smoking in chemotherapy response of patients with metastatic pancreatic carcinoma.

Statin Use and Risk of Pancreatic Cancer

Statins are widely used for the control of cholesterol levels. These drugs have emerged as potential chemopreventive agents through a variety of anti-proliferative and tumor-suppressor mechanisms. However, their use in the clinical setting has led to contradictory results regarding their efficacy in reducing the risk of developing pancreatic cancer [8-12].

In this year's "ASCO Annual Meeting", Walker et al. presented the results of their study regarding the association between statin use and the development of pancreatic cancer [14]. They included 536 patients with pancreatic cancer and 869 matched control cases. Their results showed that the use of statins (for more than 1 year prior to interview/diagnosis, for ≥ 4 days/week for ≥ 3 months) was associated with a 34% risk reduction to develop pancreatic cancer (OR=0.66, 95% CI: 0.47-0.92). Subgroup analysis according to sex, revealed a statistically significant risk reduction in men (OR=0.50, 95% CI: 0.32-0.79). Additionally, for duration of use > 120 months, the researchers found a 49% risk reduction (OR=0.51, 95% CI: 0.31-0.85) which again in subgroup analysis based on sex was found to be statistically significant only in men (OR=0.41, 95% CI: 0.21-0.80). Finally the authors tried to investigate the differential effect of the various statins used, based on their pharmacologic characteristics. The results showed that exclusive use of pravastatin was associated with reduced risk (OR=0.22, 95% CI: 0.06-0.82). Moreover, the use of high bioavailability statins resulted in statistically significantly reduced risk compared to the use of low bioavailability statins ($p=0.01$). These results suggest that the use of high bioavailability statins, especially in men and specifically in the long term, could be associated with a decrease in the risk to develop pancreatic cancer.

Discussion

Smoking has been established as a major risk factor for pancreatic cancer although the increase in risk is reported to be relatively small [4-6]. Recent data suggest that tobacco compounds do not only contribute to the development of cancer but also to the progression of the disease, rendering cancer cells more metastatic and more resistant to drugs. It has been reported that nicotine may stimulate the growth, invasion and resistance of pancreatic cells to chemotherapy through Src pathway and inhibitor of differentiation-1 (Id1) transcription factor induced mechanisms [15].

In the 2014 ASCO Annual Meeting, Ghani et al. presented the results of their retrospective study regarding the effect of smoking on treatment outcome in patients with metastatic pancreatic cancer [13]. Their findings are in line with the existing literature. They came to the conclusion that smoking may be adversely correlated with the response to chemotherapy. However, there are some concerns regarding the study. First of all, the data derive from a retrospective analysis. Moreover, the study design is not very clear. The authors arbitrarily divided the study population into "current smokers" and "non-smokers" based on cessation of smoking ≤ 2 years before the diagnosis. There are however no data regarding the number of active smokers and previous smokers in the "current smokers" group. It has been shown that the risk to develop pancreatic cancer after discontinuation of tobacco use for 5 years is reduced and is comparable to the risk of a never smoker [6]. Additionally, the results did not present any statistically significant differences between the studied groups. However, this could be attributed to the fact that the authors included previous smokers in their "current smokers group". Nonetheless, these findings are very interesting and need to be further investigated in order to elucidate the impact of smoking on the management of pancreatic cancer patients.

Apart from the factors that are associated with the development of pancreatic cancer, such as smoking, there

are also factors that may confer a degree of protection. Among them, statins, a class of cholesterol lowering drugs have emerged as potential chemopreventive agents. Their mechanism of action is mediated through various pathways and there are promising results from experimental data. However, their use in the clinical setting has not proven to be beneficial since the results from epidemiological studies are inconsistent [8-12].

The issue of statin use regarding the risk of pancreatic cancer was the topic of an abstract presented in the 2014 ASCO Annual Meeting by Walker et al. [14]. The authors found that the use of statins was associated with a 34% risk reduction to develop pancreatic cancer. This effect was more pronounced in men and especially when these agents were used in the long term (> 120 months). Moreover, the authors reported that the use of high bioavailability statins was more effective in reducing the risk of cancer compared to low bioavailability ones. The main limitation of this study is that it is based on case-control derived data. Nonetheless, these results are very important and are in line with previously published data. Khurana et al. [8] reported that statins reduce the risk of pancreatic cancer and the magnitude of this effect was associated with the duration of statin use. Similarly, Carey et al. [12] showed in a recent case-control study that statins may decrease the risk of pancreatic cancer in male smokers. However, other authors argue these findings [9-11] while the available meta-analyses [16, 17] failed to demonstrate any clear benefit from the use of statins in terms of risk reduction for the development of pancreatic cancer. The aforementioned highlight the importance of the findings by Walker et al. [14]. However, the controversy in the existing literature, mandates further research in this promising field, especially in the clinical setting, in order to better assess the effect of statins on the risk of pancreatic cancer development.

Conflict of Interest

Authors report no conflict of interest.

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