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HIGHLIGHT ARTICLE

Pancreatic Cancer: What About Screening and Detection?

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

Pancreatic cancer is the fourth leading cause of cancer-related death in both sexes in the United States. In 2013, it is expected to account for 7% of all female cancer deaths and 6% of all male cancer deaths in the USA. Late presentation of the disease and poor prognosis even after complete operative resection, justify the necessity for early detection of pancreatic cancer as well as identifying high-risk individuals (screening). Herein, the authors summarize the data presented at the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting regarding screening and early detection of pancreatic cancer (Abstracts #4045 and #4052).

What Did We Know Before the 2013 ASCO Annual Meeting?

Pancreatic cancer is the fourth leading cause of cancer-related death in both sexes in the United States [1]. In 2013, it is expected to account for 7% of all female cancer deaths and 6% of all male cancer deaths in the USA [2]. Late presentation of the disease and poor prognosis even after complete operative resection [1], justify the necessity for early detection of pancreatic cancer as well as identifying high-risk individuals (screening). Pancreatic cancer is a rare disease before the age of 45, but the incidence rises sharply thereafter [3]. The lifetime risk of developing pancreatic cancer is 1.47% (1 in 68 in men and women), based on rates from 2007-2009 of Surveillance, Epidemiology and End Results (SEER) program data [4]. Risk factors include hereditary diseases as well as environmental and other conditions [1]. As far as hereditary risk factors are concerned, it is estimated that familiar aggregation and genetic susceptibility account for approximately 10% of all pancreatic cancer cases [5]. Tersmette *et al*. performed a study in order to determine the prospective pancreatic cancer risk among first-degree relatives of pancreatic cancer patients enrolled in the National Familiar Pancreas Tumor Registry (NFPTR) [5]. The authors observed a significantly increased risk of pancreatic cancer among first-degree relatives in familiar pancreatic cancer kindreds and suggested that this group might benefit from pancreatic cancer screening [5]. Other inherited pancreatic cancer risk factors include hereditary pancreatitis, BRCA1 and BRCA2 germline mutations, Peutz-Jeghers syndrome, familiar atypical multiple mole melanoma (FAMMM) syndrome, Lynch syndrome and ABO blood type [6, 7, 8, 9, 10, 11]. Nonhereditary/environmental risk factors for pancreatic cancer include chronic pancreatitis, diabetes mellitus, cigarette smoking, obesity and *Helicobacter pylori* infection [12, 13, 14, 15, 16, 17, 18].

Although many pancreatic cancer risk factors have been well established through large studies, data concerning early detection of the disease are still inadequate. CA 19-9 has been tested as an early detection marker in pancreatic cancer, with discouraging results [19, 20]. In the study of Frebourg *et al*., for example, CA 19-9 measurement alone proved to be of no value for the early detection of pancreatic cancer [20]. Imaging techniques might be helpful in early detection of pancreatic cancer, but of limited utility for mass

Key words Early Detection of Cancer; Pancreatic Neoplasms; Risk Factors

Abbreviations CI: confidence interval; CP: chronic pancreatitis; H-L: Hosmer-Lemeshow; HS: healthy subjects; PC: pancreatic cancer

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screening purposes, mainly due to high cost [19]. Therefore, much interest has been shown in developing biomarkers for early detection of pancreatic cancer. The best surveillance strategy/screening in certain groups is another controversial, in some of its aspects, issue, but of great importance for diagnosing pancreatic cancer at an early stage.

What Did We Learn at the 2013 ASCO Annual Meeting?

Development and Validation of a Predictive Model to Assess an Individual's Risk of Pancreatic Cancer (Abstract #4045 [21])

Nam *et al*. performed a study in order to develop and validate risk prediction models within sporadic pancreatic cancer surveillance strategies. More specifically, the authors developed gender-specific risk prediction models, based on an eight-year follow-up of a cohort study with 1,289,933 men and 557,701 women in Korea who had biennial examinations in 1996-1997. Independent data of 500,046 men and 627,629 women who had biennial examinations in 1998-1999 were used in order to validate these models. Moreover, as far as discrimination and calibration abilities are concerned, the models' performance was evaluated with the use of C-statistic and the Hosmer-Lemeshow (H-L) type chi-square statistic. The model for men included age, height, BMI, fasting glucose, urine glucose, smoking and age at smoking initiation, while the model for women included height, BMI, fasting glucose, urine glucose, smoking and drinking habits. Smoking proved to be the most significant risk factor for pancreatic cancer in both men and women. When the model was validated, excellent performance was shown with C-statistics of 0.813 (95% CI: 0.800-0.826) and 0.804 (95% CI: 0.788-0.820) and H-L type chi-square statistics of 7.478 (P=0.587) and 10.297 (P=0.327) for men and women, respectively. Five risk groups were identified with hazard ratios (HR) greater than 20 in the group with the highest risk compared to the lowest one, in both men and women (Table 1).

The authors concluded that the gender-specific risk prediction models validated in their study can be used to identify individuals at high risk for developing pancreatic cancer who might benefit from increased surveillance.

MicroRNA Biomarkers in Whole Blood for Detection of Pancreatic Cancer (Abstract #4052 [22])

Schultz *et al*. performed a case-control study with two aims: firstly to detect differences in miRNA expression in whole blood between pancreatic cancer (PC) patients, healthy subjects (HS) and patients with chronic pancreatitis (CP) and, secondly, to identify panels of miRNAs for early pancreatic cancer diagnosis. More specifically, the prospective Danish BIOPAC biomarker study included 409 patients with pancreatic cancer, 33 patients with other periampullary cancers (PAC) and 25 patients with chronic pancreatitis, while 312 blood donors were included in the study as healthy subjects. Pretreatment whole blood samples were collected and miRNA expressions were investigated in three independent cohorts: 1) "Discovery study" (PC n=143; CP n=18; HS n=69); 2) "Training study" (PC n=180; HS n=199); and 3) "Validation study" (PC n=86; PAC n=33; CP n=7; HS n=44). The investigators used TaqMan® human MicroRNA assay (Life Technologies, Inc., Grand Island, NY, USA) in order to screen 754 miRNAs in the "Discovery study", while BioMark® PCR system (Fluidigm, South San Francisco, CA, USA) was used for screening 38 miRNAs in the "Training study" and 13 miRNAs in the "Validation study". In the "Discovery study", 38 miRNAs out of total 754 miRNAs in whole blood samples were found significantly deregulated between patients with pancreatic cancer and healthy subjects. These miRNAs were, then, tested in the "Training study", which resulted in creation of two diagnostic indexes: bPANmiRC index I (4 miRNAs included: miR-150 + miR-636 - miR-145 - miR-223) and bPANmiRC index II (10 miRNAs included: 6.9275 - 0.2134 x miR-122 - 0.3560 x miR-34a - 0.8577 x miR-145 + 1.0043 x miR-636 - 0.6725 x miR-223 + 0.7018 x miR-26b - 0.3233 x miR-885.5p + 1.1304 x

Table 1. Gender-specific risk prediction models for pancreatic cancer by Nam *et al*. (Abstract #4045 [21]).

Risk factors included	Men	Women
Age	+	-
Height	+	+
Body mass index (BMI)	+	+
Fasting glucose	+	+
Urine glucose	+	+
Smoking	+	+
Age at smoking initiation	+	-
Drinking habits	-	+
C-statistics	**0.813 (95% CI: 0.800-0.826)**	**0.804 (95% CI: 0.788-0.820)**
H-L type chi-square statistic	**7.478 (P=0.587)**	**10.297 (P=0.327)**

miR-150 - 0.2204 x miR-126* - 0.1730 x miR-505), with AUC 0.86 and 0.93, sensitivity 85% and 85% and specificity 64% and 85%, for the two indexes respectively (Table 2).

The authors concluded that the two diagnostic indexes identified with the use of 4 or 10 miRNAs in peripheral whole blood sample might be used as part of the evaluation of patients with non-specific symptoms, in order to diagnose pancreatic cancer early.

Discussion

The fact that patients with pancreatic cancer are usually asymptomatic till late in course of the disease in combination with low survival rates stress the importance of screening for high-risk individuals. PancPRO is the first statistical model for pancreatic cancer risk prediction in individuals with familiar pancreatic cancer. It was validated with the use of data on 961 families enrolled onto the National Familiar Pancreas Tumor Registry and its purpose was to identify pancreatic cancer high-risk individuals [23]. This year at the 2013 ASCO Annual Meeting, Nam *et al*. presented gender-specific individualized risk prediction models for sporadic pancreatic cancer, which accounts for the greater proportion of pancreatic cancer cases [21].

Screening for individuals at high-risk of developing pancreatic cancer is an important, though still controversial in some aspects, issue. Screening studies in high-risk groups have shown that preinvasive pancreatic lesions can be detected in great number of patients [24, 25]. As an example, we report the study by Canto *et al*. who performed one-time screening of 225 asymptomatic high-risk individuals, with the use of computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS). Ninety-two individuals were found to have at least one pancreatic mass or dilated pancreatic duct, by any of the imaging techniques [24]. On the other hand, Langer *et al*. performed a prospective study in order to evaluate screening of high-risk individuals from families with familiar pancreatic cancer and, based on the results of their study, came to the conclusion that general pancreatic cancer screening in high-risk individuals is not justified [26].

In 2013, International Cancer of the Pancreas Screening (CAPS) consortium met to discuss pancreatic screening. Although there was agreement in screening for high-risk individuals, consensus was not reached for the age to initiate screening, the optimal screening modalities as well as the intervals for follow-up imaging. Initial screening, though, should include EUS and/or MRI/magnetic resonance cholangiopancreatography (MRCP), not CT or endoscopic retrograde cholangiopancreatography (ERCP). The 49-expert consortium also concluded that screening and subsequent management should be performed in high-volume centers with multidisciplinary teams, preferably as part of research protocols [27].

In addition to screening, early detection of pancreatic cancer is another important and promising field in the management of this malignancy. CA 19-9 antigen is considered as one of the most favorable biomarkers in the management of pancreatic cancer, though, not useful for early detection of the disease [19, 20, 28]. According to 2006 ASCO update of recommendations for the use of tumor markers in gastrointestinal cancer, CA 19-9 should not be used as screening test for pancreatic cancer, nor as indicator of operability [29].

Since pancreatic cancer is one of the most deadly malignancies, much interest has been shown in the identification of biomarkers for early detection of the disease. A wide range of serum, pancreatic juice and tissue-based markers have been identified (CEACAM1, MIC-1, MMP-7, IGFR, PAP-2, lipocalin 2, p16, KLF6, and others), though none of the protein ones possesses the requisite sensitivity/specificity

Table 2. The Danish BIOPAC biomarker study by Schultz *et al*. (Abstract #4052 [22]).

	Discovery study	Training study	Validation study	Total number of patients
Pancreatic cancer (PC)	143	180	86	409
Chronic pancreatitis (CP)	18	-	7	25
Healthy subjects (HS)	69	199	44	312
Periampullary cancers (PAC)	-	-	33	33
No. of miRNAs screened	754	38	13	-
Method	TaqMan® human MicroRNA assay (Life Technologies, Inc., Grand Island, NY, USA)	Fluidigm BioMark® PCR system (South San Francisco, CA, USA)	Fluidigm BioMark® PCR system (South San Francisco, CA, USA)	-
Comments	38 miRNAs significantly deregulated between pancreatic cancer and controls	2 diagnostic indexes constructed: bPANmiRC index I bPANmiRC index II	-	-

to be used individually as a biomarker for the early detection of pancreatic cancer [19, 30]. The latest studies report promising results, though. In the study by Dutta *et al*., for example, serum HSP70 levels were found significantly increased in pancreatic cancer patients, which might imply possible utility in the detection of the disease [31]. This year at the 2013 ASCO Annual Meeting, Schultz *et al*. presented two miRNA diagnostic indexes in peripheral whole blood, with potential clinical value for early pancreatic cancer detection [22]. At last, Li *et al*. in their recently published microRNA analysis support the potential use of serum miR-1290 for early detection of pancreatic cancer [32].

Poor prognosis of pancreatic cancer patients makes the necessity for increased surveillance of high-risk individuals and early detection urgent. The development of biology and new experimental techniques should serve this purpose. Further studies are necessary, though, as well as high-volume centers with multidisciplinary teams in order to improve these patients' survival.

Conflict of interest The authors have no potential conflicts of interest

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