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HIGHLIGHT ARTICLE

Biomarkers for Early Detection and Screening in Pancreatic Cancer

Highlights from the "45th ASCO Annual Meeting". Orlando, FL, USA. *May 29 - June 2, 2009*

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Summary

Pancreatic cancer is the second most frequent gastrointestinal malignancy with an unabated mortality that reflects the advanced stage of presentation. Detection of early disease through screening likely is the best way to meaningfully prolong survival. The development of biomarkers for screening holds enormous promise for increasing early detection and impacting mortality. Many biomarkers have been studied including the serum protein carbohydrate antigen 19-9, vascular endothelial growth factor, and nuclear factor kappa B, however, still no blood test or other fluid analysis reliably predicts patients with disease. The authors review abstracts from the 2009 annual meeting of the American Society of Clinical Oncology, Orlando, FL, U.S.A., that report evidence for early detection using a salivary biomarker array (#4630); a mucin epitope to PAM4 (#4613); a plasma nucleotide marker of hypoxia, miR-210 (#4624); and a cleavage product of complement pathway component C3b, iC3b (#4626). The meeting featured pancreatic cancer in over 100 research abstracts, of which, four are reviewed that focus on potential markers for early detection. When applied to a population of high risk patients, biomarkers of early pancreatic cancer could provide a minimally invasive way of identifying patients that require further evaluation using endoscopic tools. These molecular beacons may even be found to be sufficiently sensitive, specific, and cost effective to be applied to a broader population of patients.

Introduction

Pancreatic cancer is the second most frequent gastrointestinal malignancy and has a median survival of less than one year with over 96% incurable at the time of diagnosis [1, 2]. In 2002, there were roughly 227,000 deaths worldwide with a mortality-to-incidence ratio of 0.98 [3]. Many biomarkers have been studied including the serum protein carbohydrate antigen 19-9, vascular endothelial growth factor, and nuclear factor kappa B, however, still no blood test or other fluid analysis reliably predicts patients with disease. The United States Preventative Services Task Force (USPSTF) does not currently recommend a screening program for average risk individuals [4], however high risk patients with known inherited predisposition are encouraged to enroll in screening and surveillance clinical trials that are evaluating an effective algorithm using endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) [5, 6, 7, 8]. Although the etiology of the malignancy remains unknown, our understanding of key molecular and tumor microenvironment events can lead to biomarker candidates for screening or surveillance.

For patients with pancreatic cancer, surgery is the only durable treatment but less than 20% of tumors are resectable at the time of diagnosis. Therefore, prognosis is improved with early diagnosis and can even be cured with resection of lesions that are less than one centimeter and without evidence of lymphovascular invasion [9]. A successful screening strategy should be attainable given the advancement in our knowledge of premalignant stages of the disease such as intraductal papillary mucinous neoplasms (IPMN) and pancreatic intraepithelial neoplasia (PanIN), advanced endoscopy techniques, and improvements in retroperitoneal-space imaging. Indeed, the disease usually rapidly progresses and given the penchant to metastasize very early in its course, assessment intervals need to be sufficiently frequent and the economic feasibility and increased complication risk needs to be brought into balance.

A biomarker that is both sensitive and specific to pancreatic neoplasia - including even IPMN or PanIN - would complement EUS and MRI modalities and if

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Abbreviations USPSTF: United States Preventative Services Task Force

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adequately safe, sensitive, and economically feasible could then be applied to a lower risk population. Screening could make a tremendous impact on this disease as pancreatic cancer is prevalent with a high morbidity and mortality, and resection at an early stage does increase overall survival. We review some of the newest developments in biomarker identification presented at the 2009 annual meeting of the American Society of Clinical Oncology (ASCO) including evidence for early detection using a salivary biomarker array (#4630); a mucin epitope to PAM4 (#4613); a plasma nucleotide marker of hypoxia, miR-210 (#4624); and a cleavage product of complement pathway component C3b, iC3b (#4626) (Table 1).

Review of Abstracts

1. PAM4

PAM4 is a purified monoclonal antibody that was generated against mucin collected from the tumor of a RIP1 xenograft and was shown in previous studies to be a marker of early pancreatic adenocarcinoma with better expression in more well differentiated *versus* less differentiated pancreatic adenocarcinomas [11, 17]. The group presented the results of additional *in vitro* immunohistochemistry, and *ex vivo* enzyme immunoassay (EIA) studies at the 2009 ASCO meeting [10]. The immunohistochemistry staining patterns with PAM4 gave a strong labeling in 92% of the mucinous cystic neoplasm samples, indicating a good affinity for this lesion. They also report that they were able to determine correlation with staining to pathologic grade of lesion. They previously reported on their EIA methodology to differentiate pancreatic cancer from pancreatitis with a sensitivity of 77% and specificity of 95% [18]. Here they carry that further and apply their EIA technique to a set of samples with known pancreatic staging (n=49; 25% stage I) and controls (n=13). The investigators were able to show an overall specificity of 82% and sensitivity of 85% calculated by ROC curve analysis. One should note that the study was limited by a small sample size and a particularly small number of patients (n=12) with stage I disease. As their previous pre-clinical work showed a difference in labeling affinity for degree of differentiation, it would be worthwhile to see correlations with histologic grade.

2. miR-210

MicroRNAs (miRs) are a class of small noncoding RNAs that regulate vast numbers of transcripts at the posttranscriptional level [19] and are emerging as important modulators of angiogenesis [20]. Specific endothelial miRs have been implicated in controlling cellular responses to angiogenic stimuli, including miR-210 which has been found to be pro-vasculogenic/angiogenic [14, 21]. Hypoxia causes increased expression of miR-210 via hypoxia inducible factor which increases vasculogenesis [14] likely by interacting with ephrin-A3 (the interaction of miR-210 on the milieu of ephrins, either inhibitory or stimulatory, has not been fully elucidated). Ho *et al*. hypothesized that miR-210 would be overexpressed in pancreatic cancer which is known to be a hypoxic environment. The group measured miR-210 in plasma from a cohort of 11 patients with known pancreatic cancer and compared to healthy controls. In the subsequent validation cohort of 12 patients, they measured a statistically significant 4-fold increase in miR-210 levels in pancreatic cancer patients. This hypothesis driven study shows promise in their early results, and larger cohorts would be helpful in further characterizing this relationship. This is a non-specific marker of hypoxia (presumably will be found in other cases of rapid tissue growth, acute or chronic ischemia, and other tumors) and would be informative to characterize the miR-210 profile with histologic grade, at diagnosis, and understand variations during treatment that may correlate with disease.

Table 1. Summary of reviewed abstracts.

Abstract # Author	Tool/Marker	Comments
#4613 [10] Gold D, *et al.*	Monoclonal antibody: PAM4	• PAM4 is an IgG1 antibody originally generated against mucin from a RIP1 murine pancreatic cancer xenograft [11]. • PAM4 identifies a "unique antigen" in precursor and neoplasia lesions. • Abstract does not specify the cancer cell's epitope or target; unclear if it has been characterized.
#4624 [12] Ho AS, *et al*	miR-210	• miR-210 is an endothelial localized pro-angiogenic microRNA. • miR-210 responds to hypoxia inducible factor and inhibits endothelial ligand ephrin A3 [13, 14]. • miR-210 is elevated in hypoxic cancers such as pancreatic, and non- specific and likely not a marker of precursor/early lesions.
#4626 [15] Marten A, *et al.*	Soluble iC3b	• iC3b is the inactivated complement component that is expressed on apoptotic cells, including pancreatic cancer cells. • iC3b binds with CR3 and acts as an opsonin and required for phagocytosis of apoptotic cells by macrophages or dendritic cells. • iC3b was elevated prior to radiographic evidence of tumor, and combining with CA 19-9 values increased sensitivity and specificity.
#4630 [16] Wong DT, *et al.*	Multiplex of mRNA of ACRV1, DMXL2, DPM1, and microbial S. mitis	• Used a human genome array to identify mRNA or bacterial signatures in saliva of patients with pancreatic cancer. • A combination of 4 mRNA markers and one bacterial biomarker gave the best sensitivity and specificity in identifying pancreatic cancer patients.

CA 19-9: carbohydrate antigen 19-9; iC3b: inactivated C3b; miR: microRNA

3. Soluble iC3b

The alternative complement pathway requires C3 and C3b for activation, and control of C3b amplification is tightly regulated by cleavage to an inactive form, iC3b. Thus, iC3b is the inactivated complement component that is expressed on apoptotic cells, including pancreatic cancer cells, which may be necrotic from treatment or hypoxic conditions. iC3b binds with CR3 and acts as an opsonin and required for phagocytosis of apoptotic cells by macrophages or dendritic cells. Marten *et al*. analyzed soluble iC3b in 232 plasma samples taken from subjects post pancreatic cancer resection, healthy volunteers, and high risk patients [15]. This prospective study followed patients with paired serum analysis and imaging every three months and reported that up to four months prior to radiographic defined recurrence, soluble iC3b plasma levels were significantly increased resulting in an AUC of 0.85 which could be further increased by combining it with the tumor marker CA 19-9 (AUC=0.92). Expression of soluble iC3b is non-specific which the investigators recognize that therefore combined their information with CA 19-9 levels. Despite its non-specific nature, expression of iC3b is especially important in understanding the interaction of a patient's immune system and tumor, as iC3b levels could reflect ability for immune tolerance to the tumor via presentation to dendritic cells [22]. This component warrants additional investigation in all clinical states including at diagnosis, during treatment, and with progression.

4. Salivary Multiplex of mRNA and Bacterial Biomarkers

Investigators evaluated the transcriptome of patients' saliva for differences between pancreatic cancer, pancreatitis, and healthy controls. They started with 11 candidate mRNAs and two microbial biomarkers and applied a logistic regression model using a combination of three of the mRNA biomarkers (ACRV1, DMXL2, and DPM1) and found a 93% sensitivity and 90% specificity for pancreatic cancer from healthy controls. Further analysis found that when they combined four biomarkers (mRNA biomarkers ACRV1, DMXL2, DPM1, and bacterial biomarker S. mitis) they could differentiate pancreatic cancer patients from all non-cancer patients (chronic pancreatitis and healthy controls) with 93% sensitivity and 85% specificity [16]. While the study is limited by a small sample size, it does demonstrate a novel and potentially important multiplex salivary biomarker panel for the non-invasive detection of pancreatic cancer.

Discussion

Pancreatic cancer meets criteria of the USPSTF and WHO for consideration of screening given its prevalence, coupled with its considerable mortality and potential for durable and meaningful disease free period when caught early and resected. The pancreas is different from other tubular parts of the gastrointestinal tract in that the retroperitoneal space is more difficult to access, sample, and image. This makes anatomy-driven modes of screening and surveillance such as endoscopy or cross-sectional imaging dependent upon availability of an experienced and technically adept physician, and widespread screening with these modalities would be cost prohibitive. Therefore, patients with high risk for disease are targeted and clinical trials have shown EUS as promising for screening and surveillance for this population [7, 23].

As screening trials for the high risk populations are ongoing with a primary focus on imaging or endoscopy, preclinical efforts are focused on identifying new biomarkers. Candidate biomarkers can be hormones, enzymes, oncofetal antigens, proteins or nucleotides that are either overexpressed in malignant or premalignant lesions or found to be unique and not in normal tissue. The 2009 ASCO annual meeting presented the data of Gold *et al*. [10] who reported an antigenic determinant that appears to be unique to cancer cells as expressed by the PAM4 paratope and could be useful in early detection. This yet undefined epitope deserves identification and classification. Marten *et al*. [15] and Ho *et al*. [12] discuss results where they saw overexpression of a complement pathway component and a pro-angiogenic nucleotide, respectively, that reach statistical significance when compared to patients without cancer, and soluble iC3b became elevated 4 months prior to radiographic progression. Wong *et al*. [16] used a multiplex model of 4 mRNAs and a bacterial biomarker that is detected in saliva and able to differentiate patients with pancreatic cancer from those with other pancreas disease or healthy controls. While these are encouraging findings, larger cohorts are needed to better gauge their sensitivity and specificity, and to understand their profile amongst the range of presentation of disease - from premalignant to poorly differentiated lesions. Furthermore, it is possible a combination of markers, as done by Marten *et al*. and Wong *et al*. and even modalities with imaging or EUS, will be needed to achieve sufficient reliability.

Discussion of candidate modalities must consider the population to target. The cause of most pancreatic cancer cases remains unknown, though several risk factors have been identified. Smoking is the most extensively studied risk factor for pancreatic cancer and was first identified in the 1960s while studying its link to lung cancer [24]. Smokers carry at least a 2-fold increased risk with a cigarette-dose-response, and 25% of all pancreatic cancer is caused by this single factor [1, 25]. Other factors that portend a high risk include advancing age, a family history of pancreatic cancer, hereditary pancreatitis, and germline cancer syndromes including Peutz-Jeghers syndrome, familial atypical multiple mole melanoma syndrome, familial breast cancer, and others (Table 2). In addition, male gender and African American race are associated with a slight increased risk. Heavy alcohol consumption may

Table 2. Risk factors for pancreatic adenocarcinoma to consider when determining populations to screen. (adapted from Rulyak [31] and Larghi *et al*. [23]).

Risk classes	Chromosome or gene	Remarks
High risk (RR ≥ 5%)		
- Family history of pancreatic cancer (Seattle cohort)	4q	Smokers develop early onset pancreas cancer [26]
- Family history of pancreatic cancer (US National Tumor Reg):		Five5 to 10 fold risk for first-degree relatives [27]
- Pancreatic cancer in ≥ 3 first degree relatives		RR = 32
- Pancreatic cancer in 2 first degree relatives		RR = 6.4
- Familial multiorgan cancer syndromes:		
- Peutz-Jeghers syndrome	STK11/LKB1	RR = 132
- Familial atypical multiple mole melanoma (FAMMM)	CDKN2a	Cumulative lifetime risk = 17
- Hereditary breast-ovarian cancer	BRCA2	RR = 5
- Familial adenomatous polyposis	APC	RR = 5
- Familial breast cancer		
- Hereditary pancreatitis	PRSS1	RR =53
- Cystic fibrosis	CFTR	RR = 32
Moderate risk		
- Male gender		
- African American race		
- Tobacco		RR = about 3 [25]
- Chronic pancreatitis		
- Hereditary breast-ovarian cancer	BRCA1	
- Pancreatic cancer in one first degree relative		RR = 4.5
- Germline diseases associated with pancreatic cancer:		
- Hereditary nonpolyposis colorectal cancer (HNPCC)	MSH2, MLH1	[28]
- Li-Fraumeni	17p	
- Ataxia-telengiectasia	11q/ATM	Breast cancer is most common tumor [29]
- Fanconi's anemia	3p, 9p, 9q,16q	[30]
Average risk (RR ≤ 1.5%)		
- Moderate alcohol use		
- Coffee consumption		

RR: relative risk

increase risk in some patients insofar as it increases risk for chronic pancreatitis, though the association between alcohol and pancreatic cancer has not been proven in multiple trials. Diabetes mellitus may be associated with pancreatic cancer, though it is hard to distinguish a cause versus effect role.

EUS and MRI can be complimentary techniques for the detection of lesions in individuals at high risk for developing pancreatic cancer and the addition of biomarkers to EUS and MRI modalities could further increase sensitivity and specificity. Results of two prospective trials evaluating EUS and MRI for high risk patients were recently presented at the 2009 Digestive Disease Week, Chicago, IL, USA. Harinck *et al*. evaluated high risk individuals (n=33) annually using EUS, MRI, and both, with investigators blinded to the alternative imaging modality [32]. Eight (24%) patients had focal lesions; detected by both EUS and MRI in 4 (12%), by MRI alone in 2 (6%), and by EUS alone in 2 (6%). The lesions missed by EUS were two simple cysts, and the MRI missed one cyst and one adenocarcinoma.

Screening for pancreatic cancer in patients at high risk often identifies neoplasms that can be resected upon the first screen. Verna *et al*. reported a prospective MRI and EUS screening of individuals with high risk for pancreatic cancer due to family history, a hereditary cancer syndrome, or familial pancreatic cancer [33]. Fifty-one patients (average age: 52 years) in 43 families completed initial testing over three years, and nine (18%) of the 51 patients had malignant or pre-malignant lesions identified in the initial round of testing that were successfully resected.

Conclusion

Detection and resection of early disease currently is the only treatment which can offer a long durable control or even cure. Shifting the preponderance of advanced stage at diagnosis to premalignant or T1 lesions through screening selected populations holds enormous promise for a favorable impact on mortality. Improved early detection screening modalities are needed and molecular beacons may even be found to be sufficiently sensitive, specific, and cost effective to be applied to a broader population of patients. Synergies are anticipated where reliable biomarker discoveries translate into a new imaging agent or therapeutic target.

Conflict of interest The authors have no potential conflicts of interest

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