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Meeting Report: Pancreatic Cancer Chemoprevention Translational Workshop

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Abstract

Pancreatic cancer is the 4th leading cause of cancer related deaths in the US with a 5 year survival rate of <10%. The Division of Cancer Prevention of the NCI sponsored the *Pancreatic Cancer Chemoprevention Translational Workshop* on September 10–11th 2015. The goal of the workshop was to obtain information regarding the current state of the science and future scientific areas that should be prioritized for pancreatic cancer prevention research, including early detection and intervention for high-risk precancerous lesions. The workshop addressed the molecular/genetic landscape of pancreatic cancer and precursor lesions; high risk populations and criteria to identify a high risk population for potential chemoprevention trials; identification of chemopreventative/immuno-preventative agents; and use of potential biomarkers and imaging for assessing short term efficacy of a preventative agent. The field of chemoprevention for pancreatic cancer is emerging and this workshop was organized to begin to address these important issues and promote multi-institutional efforts in this area. The meeting participants recommended the development of an NCI working group to coordinate efforts, provide a framework, and identify opportunities for chemoprevention of pancreatic cancer.

Keywords

Pancreatic cancer; chemoprevention; biomarkers; early detection; high risk patient cohorts; clinical trials

INTRODUCTION

The Recalcitrant Cancer Research Act of 2012 mandated the National Cancer Institute (NCI) to pursue research on cancers that have a five year survival rate of less than 20%. The overall 5 year survival rate of most pancreatic cancers is less than 10%, in great part due to the lack of early detection tests and the relative resistance to standard chemotherapy and radiotherapy regimens. Pancreatic cancer is currently the 4th leading cause of cancer related deaths in the US¹. High risk groups for the development of pancreatic cancer have been identified, and include individuals who have a family history of pancreatic cancer, contain genetic mutations that predispose to cancer (such as *BRCA2*), have new onset pancreatitis or diabetes mellitus, have pancreatic cysts identified by ultrasound imaging or cross-sectional imaging, or have had a partial pancreatectomy for a precursor lesion and are at high risk for recurrence^{2–11}. Chemopreventive/immunopreventive strategies urgently need to be developed to reduce the significant mortality and morbidity resulting from this disease.

The Division of Cancer Prevention of the National Cancer Institute sponsored the *Pancreatic Cancer Chemoprevention Translational Workshop* on September 10–11th 2015. The main goal of the workshop was to obtain information from the extramural community regarding the current state of the science and future scientific areas that should be prioritized for pancreatic cancer prevention, including early detection and intervention of high-risk precancerous lesions of pancreatic cancer. For the purposes of this workshop, pancreatic cancer was limited to pancreatic ductal adenocarcinoma. The workshop specifically addressed the following areas: 1) the molecular/genetic landscape of pancreatic precancers and cancers; 2) criteria that should be used to identify a cohort of patients at high risk for the development of pancreatic cancer; 3) determination of the most appropriate group of high risk patients that could be entered into a prevention clinical trial, 4) identification of chemopreventive/immunopreventive agents to be tested in human clinical trials; and 5) identification of potential biomarkers to assess the efficacy of preventive agent action in short term Phase II studies. While we have summarized the presentations and subsequent discussions, we have tried to capture the areas of disagreement and lack of consensus in order to emphasize those areas that will need further research. The meeting agenda has been provided as a supplement (Supplemental Digital Content, Agenda).

Keynote Speaker, Ralph Hruban: *Biology of Pancreatic Cancer*

Dr. Hruban noted that the underlying biology of pancreatic cancer and its precursors form the foundation for a rational approach to chemoprevention. Pancreatic cancer, like other cancers, is fundamentally a genetic disease and is characterized by inherited and acquired mutations in specific cancer-associated genes, as well as by changes in DNA methylation and gene expression.

Four genes are somatically targeted in the majority of pancreatic cancers (pancreatic ductal adenocarcinomas), including an oncogene, *KRAS*, and three tumor suppressor genes, *TP53*, *p16/CDKN2A*, and *SMAD4*^{12–16}. Over 90% of pancreatic cancers harbor activating point mutations in the *KRAS* gene. The *SMAD4* gene is inactivated in 55% of the cancers, the *TP53* gene in 75%, chiefly by an intragenic mutation in one allele coupled with loss of the second allele, and *p16/CDKN2A* is inactivated in >90% of the cancers. In addition to these four gene “mountains,” a number of genes are altered in a small minority of ductal adenocarcinomas, including, *ARID1A*, *ATM*, *MAP2K4*, *TGFBR2*, *ACVR1B*, *RNF43*, *BRAF*, *GATA6*, *CDK6*, *SMARCA2*, *SMARCA4*, *ROBO1*, *ROBO2*, *SLIT2*, *GNAS*, *BRCA2* and *RBM10*^{12–16}. IPMN-associated pancreatic cancers commonly harbor mutations in *GNAS* (~65% of cases) and *RNF43*. Therefore, some genetic mutations and associated altered pathways are shared among most pancreatic cancers, while other genetic mutations and associated altered pathways are seen only in a minority of the cancers.

Germline genetic changes can also contribute to the development of pancreatic cancer^{17–19}. When a familial pancreatic cancer gene is known, the risk of pancreatic cancer in carriers of a mutation in that gene can be quantified. For example, germline mutations in the *STK11* gene, which lead to the Peutz-Jeghers syndrome, are associated with a staggering 140-fold increased risk of developing pancreatic cancer²⁰. Quantifying risk is critical in designing rational chemoprevention trials: a fifty percent reduction in the incidence of pancreatic

cancer in the general population (whose risk is only 9 per 100,000 per year) may be impossible to detect, while a 50% decline may be measurable in individuals with a germline *STK11* mutation. In addition to increasing the risk of pancreatic cancer, almost all known familial pancreatic cancer genes, with the exception of *PRSS1*, are associated with an increased risk of extra-pancreatic malignancies. Thus, with effective chemopreventive efforts we have the opportunity of saving lives by decreasing the incidence of both pancreatic and extra-pancreatic malignancies.

Aberrant methylation is common in pancreatic cancer²¹. This aberrant methylation, because it is potentially reversible, is a potential target for chemoprevention efforts. It has been suggested that tests designed to detect aberrant methylation could be useful approaches to the early detection of pancreatic neoplasia because many methylation events appear to occur early in the development of pancreatic neoplasia^{22,23}. The expression of a number of microRNAs is also altered in pancreatic cancer and its precursors, and again, it has been suggested that these alterations could form the basis for the early detection of pancreatic neoplasia^{24–26}. All of these changes in gene expression ultimately are associated with changes in protein expression, and these alterations in protein expression can form a foundation for a rational basis for chemoprevention and early detection²⁷.

An understanding of the precursor lesions that give rise to invasive pancreatic cancer is central to any chemoprevention strategies. A growing body of evidence suggests that invasive ductal adenocarcinoma usually arises from one of three pathologically defined precursor lesions; pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs)⁹. PanINs are small microscopic lesions, while IPMNs and MCNs are larger macroscopic lesions that can be detected on imaging. PanINs, IPMNs, and MCNs harbor many of the same genetic alterations as are found in invasive ductal adenocarcinomas, helping to establish that they are indeed precursor lesions. Of note, some of the alterations, such as telomere shortening and mutations in *KRAS*, appear to be early events, while other alterations, such as the inactivation of *TP53* and of *SMAD4*, are late events^{25,28,29}. The timing of these alterations is important because early events may be most suitable for true prevention while late events - those that occur in precursor lesions with high-grade dysplasia - may be more suitable for early detection efforts. Current investigation suggests a latent period of at least 10 years before the development of pancreatic cancer³⁰.

The histopathology of precursor lesions may also provide insight into chemoprevention approaches. For example, inflammation can be found associated with even the smallest precursor lesions. This inflammation may incite parenchymal atrophy and fibrosis, and it has been hypothesized that inflammation may also promote further expansion of the neoplastic precursor lesions. This vicious cycle of epithelial proliferation, inflammation, more epithelial proliferation, and more inflammation, *etc.* could be a reasonable target for chemoprevention^{31–35}.

Histopathologic studies have also demonstrated that IPMNs are often multifocal, a finding that, as will be discussed later in greater detail, suggests that chemoprevention could be used to prevent metachronous disease in selected patients³⁶.

In summary, the biology of pancreatic cancer and its precursor lesions forms a rational basis for chemoprevention of pancreatic cancer. The biology defines whom to target with chemoprevention efforts, and it provides insight into how they should be targeted.

Session 1: Targets and Surrogate Biomarkers that can be Measured During Pancreatic Precancer to Cancer Progression

Peter Allen: *Overview of Biomarkers for Early Pancreatic Cancer Detection*

Dr. Allen reviewed the dismal statistics for pancreatic cancer patients, noting the aggressive biology, late stage at diagnosis, and general ineffectiveness of systemic therapies both in the adjuvant setting and in the setting of advanced disease. With current diagnostic technology we do not have the ability to identify early pancreatic cancer; thus, the benefits of diagnostic biomarkers for early detection in pancreatic cancer will not be realized until lesions can be identified that have not developed micro-metastatic disease. A problem is that PanIN lesions are too small to be identified by current cross-sectional imaging techniques. However, features of chronic pancreatitis can be identified that correlate with the presence of multifocal PanIN lesions. When strict criteria are implemented³⁷, one can obtain 85% accuracy of endoscopic ultrasound (EUS) for identifying chronic pancreatitis. However, the accuracy of EUS in identifying the chronic pancreatitis changes suggestive of multifocal high-grade PanIN is unknown.

IPMN is a grossly identifiable cystic precursor lesion of pancreatic cancer. IPMNs can be identified by their radiographic characteristics and elevated cyst fluid levels of carcinoembryonic antigen (CEA) as well as mutant alleles of the *KRAS*, *GNAS*, and *RNF43* genes³⁸. Currently, operative resection is recommended when there is a presumed risk of high-grade dysplasia or invasive disease (high-risk lesion), such as when the main pancreatic duct is dilated on cross-sectional imaging^{39,40}. However, we need more accurate markers of high-grade dysplasia. These could be obtained using clinical and radiological criteria as well as biomarkers from cyst fluid, sera, or tissue. Recent studies have found that while oncogenic gene mutations isolated from cystic fluid are imperfect markers for the degree of dysplasia, mutations in *KRAS* and *GNAS* are found in a high percentage of IPMNs, and *SMAD4* and *TP53* alterations suggest the presence of high-grade dysplasia⁴¹.

Proteins involved in inflammatory pathways have also been found to be associated with the degree of dysplasia and may serve as potential prognostic markers. Increases in the cystic fluid expression of the mucins MUC2 and MUC4⁴² and cytokines such as IL1b, IL5, and IL8⁴³ could distinguish carcinoma and high-grade dysplasia from lesions with low- and intermediate-grade dysplasia. Recent studies have suggested that the presence of tumor infiltrating neutrophils in the cystic fluid can predict the degree of tissue dysplasia⁴⁴. With this evidence that inflammation contributes to pancreatic tumor development, a panel of inflammatory associated proteins overexpressed in cystic fluid was used to develop prognostic models for high-risk IPMN patients⁴⁴. Ancillary approaches such as mutational analyses and markers of inflammation may be combined with clinical and radiological parameters to develop nomograms to predict the risk of the presence of high grade dysplasia⁴⁵. Importantly, such approaches need to be tested in a validation cohort.

The key question is who to target. If we target “early” pancreatic cancer patients, we minimize the possibility of overtreatment but early lesions cannot be reliably detected. Precursor lesions such as PanIN are the most common pathway to PDAC but are difficult to detect by imaging or EUS. PanIN-3, the immediate precursor lesion to PDAC, is a diagnosis made at histology. IPMN is radiographically identifiable but is a relatively uncommon pathway to PDAC.

Michael Goggins: *Molecular Biomarkers for Early Pancreatic Cancer Detection*

Dr. Goggins echoed some of the issues raised by Dr. Allen in that the best surrogate end points for a chemoprevention study for patients at risk of pancreatic neoplasia are the common precursor lesions, PanINs and IPMNs, but he emphasized that detecting and quantifying these lesions is not straightforward.

Most pancreatic cancers are thought to arise from PanINs so the preferable chemoprevention target should be PanINs and ideally target both PanINs and IPMNs. Since low-grade PanINs and IPMNs are common and have a low rate of progression, a chemoprevention agent need not have to cause the prevention or regression of PanINs and IPMNs, it merely needs to prevent the progression of these lesions from low-grade to high-grade lesions and to invasive cancers in order to be very effective. Currently it is difficult, if not impossible, to determine which PanINs and IPMNs will progress, and which are indolent and will not progress.

Pancreatic imaging using magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) and EUS can quantify IPMN lesions, but these imaging tests cannot identify PanINs and they cannot grade IPMNs. Histological examination of pancreatic lesions is therefore the optimal endpoint of a chemoprevention study until an adequate surrogate biomarker can be developed. A practical study design for a chemoprevention trial would be to treat patients who are candidates for surgical resection based on the presence of a lesion suspected to be an IPMN. Patients could be preoperatively randomly assigned to receive the chemoprevention agent *vs.* placebo; PanINs and IPMNs would be counted, graded, and their size determined in the subsequent resection specimen by pathologists who would be blinded to the treatment arm. The numbers of neoplastic lesions could then be compared in the treatment versus placebo groups. Patients with sporadic or familial forms of the disease could be included, but familial cases would be preferable as they are more likely to have multiple precursor lesions. These familial cases are somewhat analogous to choosing patients with familial adenomatous polyposis (FAP) for a chemoprevention study to evaluate the role of the agent for colonic adenomas.

In contrast to familial cases, patients with sporadic disease who undergo resection of a single large pancreatic cyst suspected to be an IPMN have a ~15–20% probability of having a serous cystadenoma, a lesion with almost no neoplastic potential. It is obviously desirable to avoid treating these patients. As noted by Dr. Allen, this problem could be potentially avoided by molecular analysis of the pancreatic cyst fluid (which is not routinely done in the clinic at present) to confirm that a pancreatic cyst is a mucinous neoplasm. However, one of the concerns about concentrating on the neoplastic nature of a particular pancreatic cyst is that one can ignore the rest of the pancreas, and some patients with pancreatic cysts who develop a pancreatic cancer have a cancer that did not arise from their cyst⁴⁶. These cancers

are thought to arise from metachronous and synchronous undetected PanINs. Genetic analysis of pancreatic juice is a potential approach to estimating the neoplastic burden of the whole pancreas because a lot is known about the relationship between gene mutations and the grade of neoplasia. Ideally, pancreatic juice analysis would be performed to detect mutated oncogenes and then compared to the histological quantification of neoplasia at resection^{47–49}.

Familial pancreatic cancer (FPC) cases with multiple cystic lesions may be the best candidates for a chemoprevention trial because they often have numerous precursor lesions^{50–52} and they have a significantly increased risk for developing pancreatic cancer. An alternative to enrolling these subjects (family history of pancreatic cancer, have multiple pancreatic cysts, and are candidates for surgery within the next 6–12 months) is to enroll familial subjects with cysts, who will undergo clinical surveillance but would not be undergoing surgery within the next 6–12 months. These patients would be evaluated by pancreatic imaging and pancreatic juice analysis without the endpoint of histology. The endpoint would be changes in the number and size of pancreatic cysts and changes in the mutational burden of pancreatic juice.

Another study population that is somewhat less attractive is those sporadic patients who have undergone pancreatic resection for an IPMN and are at risk for developing another cancer over the next few years (estimates of ~10% in several series^{36,53}). The challenge with these cases is that after surgery they may have changes in their pancreas related to the surgery that can mimic metachronous disease (such as main duct dilatation).

Discussion Questions (posed by Mark Miller, NCI)

1. How does our knowledge of the biology of pancreatic disease progression help identify potential biomarkers?
2. *What possible preventive intervention-related biomarkers (e.g., PGE₂, cytokines) and early disease markers (e.g., pancreatic function tests such as peak bicarbonate/fecal elastase, circulating tumor DNA, inflammatory markers, imaging, mutations in pancreatic juice, etc.) should we use as primary/secondary endpoints?*
3. What possible biomarkers can be used for short-term “window of opportunity” or “proof-of-concept” trials?

Summary of Session 1 Discussion

- The prevalence of PanIN lesions increases in the general population as it ages, but clearly most people with PanINs don't develop pancreatic cancer⁵⁴. There have been a number of prospective studies in which patients with clearly defined IPMNs on imaging have been followed for long periods of time, and most don't develop an invasive carcinoma^{36,53}. The so-called switch is not known at this time, but identifying and preventing it would have significant impact. Peter Allen mentioned the role of inflammation, and in some PanIN or some IPMN lesions,

chemoprevention/immunoprevention could prevent the development of a possible vicious cycle in which, as the lesion grows, it induces an inflammatory cell infiltrate, injuring the epithelial cells, which causes injury and repair and more proliferation, which causes more inflammation. Multifocality in IPMNs is well-defined, and synchronous and metachronous disease need to be considered when planning a chemoprevention approach.

- A sporadic IPMN cohort may be ideal for a chemoprevention trial, because patients who have an IPMN resected have a significant risk (10% or even more) of developing a carcinoma in their remnant pancreas^{36,53}. This seems to be a well-defined population that has a significant enough cancer risk that, whatever is done for chemoprevention, there will be a measurable outcome. Large centers with large enough patient populations could provide a multi-institutional cohort for the study. Another cohort for chemoprevention trials would be patients with a strong family history of pancreatic cancer, and those with a known germline variant that predisposes to the development of the disease. These high risk individuals have a very significant risk of developing pancreatic cancer, including those with well-defined genetic risk due to germline mutations in *BRCA2*, *PALB2*, *ATM*, or Peutz-Jeghers syndrome, the incidences of which are fairly well defined in some cohorts. The use of these two different cohorts (sporadic IPMN versus familial pancreatic cancer patients) in chemoprevention trials may be applied for two somewhat different questions. In the case of IPMN, chemoprevention would be used to prevent pathology established lesions from progressing. In the familial case, pathology may not be available for patients who have not had pancreatic surgery; thus chemoprevention would be used to prevent the progression to invasive cancer over time. In the latter case the size of the cohort may need to be quite large and the time of the trial may need to be long in order to detect the endpoint of invasive cancer. Another consideration for these differing cohorts is that the preneoplastic lesions differ (IPMN versus PanIN) and the effect of chemoprevention in one setting may or may not apply to the other setting.
- A third group that may not have been touched upon are just high-risk IPMN patients before resection. There haven't been many chemoprevention studies of IPMN progression to invasive cancer, mainly because we don't have the preclinical models. In the IPMN group, one of the risk factors for recurrence is a family history of pancreatic cancer. The genetically-defined high-risk groups are going to have to undergo some type of pancreatic screening to detect precursor lesions. So, if patients are going to be screened and followed, the investigator would want to potentially limit the group to a well-defined group with these precursor lesions. One of the advantages of that IPMN group is the ability to monitor change. Patients who progress can be detected by access to the fluid that's

within the cyst; looking and assessing the fluid as well as the cyst wall would be the ideal biomarker which provides information on the entire pancreas. It is important to point out that a biomarker that is present in cyst fluid that differentiates cancer vs. non-cancer (other than cytology) has yet to be clearly identified and validated

- An important point brought up in the panel discussion related to what would be the ideal readout for a chemoprevention study. In the current state, the incidence of invasive cancer is the only definitive readout available. It is clear research in the development of an early detection biomarker for pancreatic cancer (either blood-based or imaging modality) will be needed to more effectively carry out chemoprevention studies in high risk patients. Variations in CT technique can change the apparent cyst size, and, if there are multiple cysts, it can be difficult to figure out which cyst is which. There are other surrogate markers, some of which have been mentioned (for instance, the genetic and inflammatory markers presented by Dr. Peter Allen).
- An additional point that was brought out in the discussion was the relationship between inflammation and the development of pancreatic cancer. Data have shown that in the very low-grade dysplasia lesions which have been resected, we don't see any inflammatory cell infiltrate; it was almost zero, or one percent⁴⁴. On the other hand, one of the biggest risk factors in familial pancreatic cancer is genetic alteration of the *PRSS1* gene which results in hereditary pancreatitis⁵⁵. It is a hereditary pancreatitis gene, and those patients have a 25–40% risk of cancer. So, clearly, inflammation is important.
- There have been a number of studies that have shown if you treat with an anti-inflammatory agent at the right time point, at least in the preclinical models, you can prevent cancer in mouse models that otherwise have almost 100% penetrance of a first cancer. Timing is important, because if you treat mice with mPanIN-3 lesions, chemoprevention may not work. It is pretty well established that inflammatory infiltration drives progression from late-stage PanIN-2. A lot of the agents that we might want to use for a chemoprevention might already be used on some of these patients. However, when and how do you measure the inflammation?
- Some agents have shown strong efficacy pre-clinically and are powerful agents for pancreatic cancer prevention, but clinically we don't know which one to use first. We may only be able to run one or two small trials because FPC cohorts are relatively uncommon. It will be important to decide which agent(s) is the top priority. Since some of these agents, like aspirin, are already used in this patient population, we may have ongoing clinical trials actually taking place. It may be possible to look retrospectively and see if these patients have different outcomes in terms of tumor progression or latency.

Session 1 ended with a final discussion regarding the need to define the right patient population(s). There is a need to find a genotype/phenotype link that can tie genetic mutations to cancer incidence. These could be familial patients who have lesions or a certain subset of IPMN patients. One would not want to enroll people who might get cancer in six months. The high-risk population is developing the disease earlier and they have extensive imaging abnormalities; they have PanINs, IPMNs, and visible lesions. Some of these lesions may be measurable as cysts.

Session 2: How Best to Identify High-Risk Individuals Early in their Disease Progression

Gloria Petersen: *Overview of High Risk Patient Cohorts / Epidemiologic Data (Vitamin D, metformin, statins, aspirin etc.)*

Based on epidemiologic data, there are several non-specific factors that are known to influence pancreatic cancer risk. These include age (older), smoking, family history of pancreatic cancer, race (African American), obesity (high body mass index), diabetes mellitus history, chronic pancreatitis history, diet (meat cooking/preparation), and heavy alcohol use. The majority of pancreatic cancer (70%) is sporadic, with no known cause. The role of genetic polymorphisms or gene-environment interactions is being actively studied to try and identify the associated factors. It is estimated that 20% of pancreatic cancers that are sporadic exhibit an early age of onset (<60 years of age). Familial pancreatic cancer accounts for approximately 10% of cases, and only 2% of pancreatic cancer is associated with uncommon hereditary syndromes (*e.g.*, Peutz-Jeghers syndrome). The conundrum is that pancreatic cancer is not common (12.3/100,000⁵⁶) and it is not a common complication of pancreatic disease. Studies indicate the prevalence rate of mucin-producing adenocarcinoma in patients with pancreatic cysts was 33.2/100,000⁵⁷.

To detect pancreatic cancer at a curable stage, high risk, asymptomatic individuals need to be screened. Patient stratification is important. Broadly, two categories can be defined, individuals with and without pancreatic disease. Individuals with no pancreatic disease who are at increased risk include the following: 1) Family history, seen as two or more first degree relatives (3-fold higher); 2) Carriers of certain genetic mutations are at higher risk; 3) Individuals with recent onset diabetes mellitus (8-fold higher); 4) Other cancers such as breast cancer or melanoma; 5) Age, race, and BMI (body mass index); and 6) Exposures such as diet (meat), heavy alcohol use, and smoking (Table 1). Individuals with pancreatic disease who are at risk include those with the following conditions: 1) Hereditary (53-fold) or chronic pancreatitis (4- to 8-fold); 2) Mucin-producing cysts in the pancreas (*i.e.*, IPMNs and MCNs); and 3) Hereditary syndromes (*i.e.*, Peutz-Jeghers syndrome, 132-fold).

The effects of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen have been studied to determine if there is any chemopreventive effect on the development of pancreatic cancer⁵⁸. The study determined that aspirin use (1 day/month or greater) was associated with a significantly decreased risk of pancreatic cancer (OR=0.74, 95% CI: 0.60–0.91, P = 0.005) compared with never or less than 1 day/month. Furthermore, the study concluded that it was the aspirin use, but not non-aspirin NSAID use, that was associated

with the lowered risk of developing pancreatic cancer. Another study found similar effects: regular use of aspirin was protective against pancreatic cancer⁵⁹ (OR=0.52). In addition, a decreasing risk of pancreatic cancer was observed for each year of low-dose or regular-dose aspirin use⁶⁰.

A significant number of individuals take statins to lower cholesterol levels. Statins have been studied for potential chemopreventive effects on pancreatic cancer with mixed results. One study determined that ever use of statins reduced the risk of pancreatic cancer⁶¹ (OR=0.66). When stratified by sex, statins significantly reduced pancreatic cancer in men (OR=0.5). The duration of use of the statins was inversely associated with the pancreatic cancer risk, with an overall OR=0.51 with a >10 year use of statins. Another study showed differential effects of statins on the risk of developing pancreatic cancer⁶². Overall, the study concluded that there was no association between regular statin use and reduced pancreatic cancer risk (OR=0.82); this included patients with Type 2 diabetes mellitus. A significantly reduced risk for pancreatic cancer (OR=0.11) was seen in male smokers with regular statin use. The role of statins in pancreatic cancer needs to be further explored and clarified. Current epidemiological data on chemoprevention suggest that aspirin and statins have potential chemopreventive effects on pancreatic cancer, while Vitamin D shows conflicting data and metformin has no convincing effect.

Teresa Brentnall: *Molecular Tests for Identifying High Risk Patients*

Patients can be risk-stratified based on family history (number of family members with pancreatic cancer) and inherited gene mutations. The relative risk for individuals with a family history of pancreatic cancer ranges from 2–3 fold if they have one family member with pancreatic cancer, to as high as 14 to 32-fold for individuals with >3 family affected family⁶³. Besides this, other risk factors can include smoking, diabetes mellitus, and a personal history of cancer. This presentation will focus on patients defined as high risk because of familial pancreatic cancer (FPC). At the highest risk for pancreatic cancer are the FPC patients who have abnormal pancreatic parenchyma or IPMN lesions on endoscopic ultrasound (EUS) or other imaging⁶⁴.

What could be the target lesion(s) for chemoprevention trials? In the general population, with no previous history of pancreatic cancer, autopsy and surgical studies show that PanIN-1 is common, PanIN-2 is uncommon, and PanIN-3^{54,65–67} is extremely rare. In patients with FPC, both IPMNs and PanINs are found with greater frequency and at higher grade⁶⁸. In the following scenario, surveillance should be considered if a genetic predisposition to pancreatic cancer exists (*i.e.*, > 2 family members with pancreatic cancer). The standard biomarker tests, CA19-9, CEA, and CT imaging are not sensitive enough to detect pre-symptomatic pancreatic cancer or precursor lesions, such as PanIN-3s. Consensus guidelines for pancreatic screening have been developed including what tests should be used (EUS and MRI/MRCP) and which risk groups are appropriate for pancreatic screening. Because the evidence demonstrating the benefit of pancreatic screening is limited, pancreatic screening is best performed as part of a clinical research protocol. Many centers rely on EUS as the primary screening test as it is the most accurate test for detecting small solid pancreatic lesions and has similar accuracy as MRI/MRCP for detecting pancreatic cysts⁵.

Some centers alternate MRI/MRCP with EUS or use MRI/MRCP as a primary screening test with EUS to further evaluate the pancreas if the MRCP is abnormal. CT scans of the pancreas are generally not used as primary screening tests but can be valuable if there are pancreatic imaging abnormalities detected by EUS or MRI/MRCP that raise the possibility of cancer. In earlier protocols ERCP was used to evaluate pancreatic ductal abnormalities, but the role of ERCP has been largely superseded by MRCP⁶³. The Seattle group gained experience with performing a pancreatic tail resection in cases where there was concern for advanced PanIN based on pancreatic imaging. This enabled the grading of any PanIN lesions detected. In their series total pancreatectomy was considered for patients with advanced PanIN, particularly if the patient had insulin-dependent diabetes mellitus. In an unpublished study from the Seattle group, 100 high risk patients with an extensive family history of pancreatic cancer were followed. Within this group, 22 patients had both an abnormal EUS and abnormal ERCP/MRCP. For these select patients, pancreatic tissue was resected to obtain a histologic diagnosis. If there was a clear cut mass or IMPN, that tissue was targeted through laparoscopy; in the absence of a targetable lesion, the pancreatic tail resection was performed. Because the histologic changes are widespread and multifocal, it is typical for the entire pancreas to be affected with PanIN lesions. Once the diagnosis and grading of neoplasia is completed, decisions can be made about the value for future removal of the pancreatic remnant for treatment of advanced PanIN or high-grade IPMN. In that group of 22 patients with abnormal imaging at EUS and ERCP/MRCP, 21 patients underwent surgery for diagnostic purposes: 4 had a partial pancreatectomy (3 PanIN-2 lesions) and treatment (1 invasive cancer). In these patients the pancreatic remnant remains intact. Another 17 had completion of total pancreatectomy (5 FPC patients with widespread PanIN-2 lesions accompanied by insulin-dependent diabetes and 12 FPC patients with PanIN-3 lesions). Patients with PanIN-2 lesions who already had insulin-dependent diabetes preoperatively could consider completion of the pancreatectomy per their preference, because loss of the remnant would not cause a new problem for these patients. For FPC patients with PanIN-2 lesions who did not have diabetes, completion of the pancreatectomy was not offered as an option.

Did this early detection strategy improve patient outcome? Of the 20 patients in the dysplasia group who underwent surgery, no new pancreatic cancer developed post-operatively (1–10 year follow-up). Two patients developed PDAC while in surveillance, one patient who was late in follow-up for surveillance had a 2 cm cancer with metastatic disease and died within 2 years, while the other patient had a resectable cancer and is alive after 7 years. In the 78 non-surgical cases, there is no evidence of disease and no pancreatic cancer has been detected. This cohort underscores the difficulty with PDAC surveillance strategies that use currently available imaging technologies. Clearly newer methods that can detect PanIN3 are needed.

In the search for biomarkers to detect pancreatic cancer, plectin was recently identified and used as a molecular marker for imaging⁶⁹. Plectin is a cytoskeletal protein found on the surface of epithelial cells. Plec1 was tested as an imaging target. Plec1-targeting peptides (tPTP) were used as a contrast agent for single photon emission computed tomography in a murine model of PDAC. *In vivo* imaging with tPTP was able to detect primary and metastatic pancreatic tumors. This imaging method may also detect preinvasive mPanIN-3

lesions. In addition to examining the epithelial cell surface for identifying imaging targets, the cancer associated fibroblasts were also examined. Cancer associated fibroblasts (CAF) consist of activated fibroblasts or myofibroblasts, are found in stroma surrounding solid tumors, and promote invasion and metastasis of cancer cells⁷⁰. A cytoskeletal protein, palladin, is essential for cell motility and palladin is markedly overexpressed in the CAF surrounding PDAC and PanIN-3, while it is absent in the fibroblasts of normal pancreas or chronic pancreatitis⁷⁰. In pancreatic cancer, it has been suggested that palladin activates the transition of stromal fibroblasts into myofibroblasts during the early stages of tumorigenesis and its aberrant expression increases with neoplastic progression. Targeting CAF using palladin could be another molecular target for SPECT and PET imaging.

Another promising technology is molecular ultrasound to enhance cancer imaging by detecting abnormal vasculature with pancreatic tumor formation. New markers with the ability to bind to neovascular proteins in pancreatic cancer have been identified. Using proteomics studies of PDAC, thymocyte differentiation antigen 1 (Thy1 also known as CD90) was identified as a marker associated with the neovasculature of pancreatic cancer⁷¹. Molecularly targeted contrast-enhanced ultrasound (molecular ultrasound) is a new technique with the potential for detecting molecular markers on the neovasculature of pancreatic cancer. This technology uses modified microbubbles which bind to molecular markers. This study validated the use of this technology and Thy1 as a molecular imaging marker for detecting PDAC in mouse models. Thy1 expression was also detected in the vasculature of mPanIN-3 lesions. The earlier stages, mPanIN-2 and mPanIN-1 lesions had lower expression of Thy1. These results look promising and suggest that Thy1 may improve the likelihood of detecting mPanIN-3 lesions. Additional PanIN-3 markers are being developed, including TIMP1⁷² (tissue inhibitor of metalloproteinases-1) as well as the urinary markers, LYVE1 (lymphatic vessel endothelial hyaluronan receptor 1), REG1A (regenerating family member 1 alpha), and TFF1 (trefoil factor 1) for these precursor lesions⁷³. Finally, some studies are exploring the use of circulating tumor cells (CTCs), exosomes, and circulating tumor DNA⁷⁴ (ctDNA) as biomarkers for pancreatic cancer⁷⁵. The molecular characterization of CTCs can provide information on pancreatic lesions that are difficult to biopsy.

Potential scenarios for chemoprevention that target of high-risk patients—A potential scenario for a chemoprevention trial that monitors high-risk patients, in the absence of an intermediate biomarker for pancreatic cancer, can use current imaging techniques as a surrogate for histology. The strategy would presume that patients who have recurrently normal EUS exams likely do not have advanced neoplasia, whereas FPC patients who have clear cut abnormalities at EUS would be considered to have pancreatic inflammation, higher-grade neoplasia (PanIN-2 or -3), or both. Such a chemoprevention trial design would need to take that into account by using imaging-based risk stratification, the patients would likely be at different stages of neoplastic progression. For FPC patients with a normal EUS, the potential chemopreventive agent needs to have a minimal side effect profile because the trial time (development of pancreatic cancer) may be long and presumably the pancreas is in the very earliest stages of neoplasia. For the highest risk patients, who have an abnormal EUS or cystic lesions, the potential chemopreventive agent needs to be highly efficacious

because neoplastic progression may have already started; in this case the trial time (development of pancreatic cancer) may be short. A placebo arm would be necessary for either the highest risk cohort or the lower risk cohort, and imaging changes would be followed over time to be measured as the outcome.

A second potential trial for targeting of high risk patients can include a molecular imaging marker. The patient population would consist of high risk patients with the presence of PanIN-3 lesions, as confirmed by an imaging molecular marker. This can be set up as a randomized trial or, alternatively, allow patients to self-select for chemoprevention versus surgery. This would likely be a short term trial, so the chemoprevention agent can be highly efficacious and some side effects would be acceptable. Serial imaging will be done at short intervals to determine if an effect was produced by the agent. The outcome would include quantitative measures of any changes detected by imaging versus the development of cancer.

A third scenario is a cohort of IPMN patients which had PanIN-3 lesions in their resected pancreas. In this type of study, these patients will be randomized to either a chemopreventive agent or placebo and then followed by annual EUS. The outcome would be pancreatic cancer.

There are several problems to consider for a chemoprevention trial. The highest risk patients are those with PanIN-3 lesions, yet these lesions are relatively rare and impossible to detect without surgery. The natural history of these lesions is unknown, so the progression of PanIN-3 to invasive pancreatic cancer is not well elucidated. Furthermore, a histopathological diagnosis of PanIN-3 is needed and this requires pancreatic tissue. Finally, EUS is very operator dependent and imaging technologies cannot detect these lesions. Future imaging technologies, including molecular PET-CT and molecular ultrasound, have the potential for improving the likelihood of detecting significant PanIN lesions.

Discussion Questions (posed by Mark Miller, NCI)

1. What clinical cohorts can we successfully identify and recruit for clinical trials? Do we want to pick a very specific subset (for example, IPMN patients that can be imaged, pancreatitis patients, etc.) or cast a broader net and look at patients with different risk factors/histories?
2. How many patients will we need and how many can we successfully recruit into a trial?
3. Is there any evidence that potential agents have shown activity in a clinical setting?

Summary of the Session 2 Discussion

- The high-risk FPC population who are currently in surveillance would be a good cohort to consider for chemoprevention trials. These patients are very motivated and many of them are followed for long periods of time. This would be a cohort where current imaging or molecular biomarkers of neoplasia would be followed as an endpoint. Depending on statistical modeling, it may be necessary to enroll fairly larger numbers of patients to

have enough events. Through collaborative studies, it is possible to combine FPC cohorts at a variety of centers; however the costs of such a study could potentially be high.

- As stated above, the cost of a chemoprevention trial can be high given the large number of patients and the long time frame that might be required. Identifying a smaller, high risk cohort for a chemoprevention trial would lower the cost. Ideally, this is a very high-risk population whose lifetime risk would be 25% or more based on aggregate environmental and genetic factors. One could then decide whether you use EUS or not. If you did use EUS and it was abnormal, that would indicate an increased risk for the development of pancreatic cancer. One could use the more economical hemoglobin A1C levels, which might also provide data supporting an increased risk. The time frame of the study would also influence the costs. We are not doing a lifetime study here. Would 5 years be sufficient to see an effect? For example, you can have a lifetime risk of 25% of getting PDAC which is quite high, but if the five-year risk is two percent, then all your studies are going to be negative. These patients have to be in the age range where they are likely to get cancer.
- Another group that could be considered for chemoprevention trials would be to take advantage of the large registries of the *at-risk relatives* of individuals who have had PDAC. In such a setting, many of these at-risk relatives are not in surveillance and thus, the end point would be development of PDAC, rather than imaging changes after intervention versus placebo.
- Dr. Peter Allen also made a strong case for certain subgroups of patients with sporadic IPMNs, particularly those who have had surgery and have a ten percent likelihood of progression over four years, which is high. The familial pancreatitis group could be considered as well but, they're a very specialized group. We would have to include clinical imaging or some type of screening/surveillance protocol.
- There are a lot of at-risk relatives in these registries who enroll, but the full development of that cohort has not been realized because there hasn't been that level of support. If you were going to study a familial group, you would have to expand it. I think they would participate in cohorts if we have them. I think the issue is that we need the resources to develop those.
- There are other sources of high risk groups beyond the pancreatic cancer surveillance programs or generalized PDAC registries. There are gene-specific registries of BRCA-2 positive families, of which a subset feature a risk for pancreatic cancer. Many of these BRCA families will have predominantly breast and ovarian cancer; however, it would be possible to select those family members that came from families where there was at least one pancreatic cancer. The same thing would be possible with a familial atypical mole and melanoma cohort. There are melanoma

registries, one of which is here at NCI. The Large Consortium Melanoma definitely has some pancreatic cancer patients because they were the first ones to make the observation that pancreatic cancer in these families was associated with *CDKN2A* mutations.

- If you do a two, three, or four year study to prevent cancer, the immediate concern is that the cancer was already present at the start of the trial. You are actually not preventing, you are treating an established cancer. That's a very legitimate and cogent reason for not picking cancer as an endpoint in a short-term study, because even if the agent is effective in chemoprevention, the study could produce a false negative. This is a real impediment and the question is whether there is a way to get around it?
- There is an overlap with early detection, biomarkers, and assays. In the setting of chemoprevention, what we are looking for are biomarkers of disease activity which likely will overlap with early detection.

Session 3: Agents and Pathways That Could be Targeted in a Prevention Trial

Chinthalapally Rao: *Overview of Preventive Agents for Pancreatic Cancer*

Pre-invasive precursors such as PanINs, IPMNs, and mucinous cystic neoplasms (MCNs) progress slowly over many years to decades to develop invasive pancreatic cancers^{4,8,9,15}, thus there is a time frame of several years for effective prevention/intervention strategies⁷⁶. Molecular pathobiology has provided a compendium of genetic lesions, often implicating aberrant molecular changes at genetic, transcriptomic, epigenetic, and proteomic levels that correlate with histological progression from normal to non-invasive precursor to invasive carcinoma^{77–81}. This has led to the development of several complex genetically engineered mouse models (GEMMs) of pancreatic cancer that recapitulate key aspects of human pancreatic cancer development, including the development of precursor lesions in the pancreatic ducts. Most of the established GEMMs are driven by activation of oncogenic *KRAS* (*KRAS*^{G12D}) using the expression of *Cre* recombinase from the pancreatic specific promoters Pdx1 or Ptf1a/p48. These promoters in the developing pancreas define both endocrine and exocrine progenitor cell populations. While expression of mutant *KRAS* by itself is sufficient to generate the entire histological spectrum of mPanIN lesions, the penetrance of invasive cancer, the time for progression to invasive cancer, and the predominant histology of the cancers that arise vary depending on additional genetic alterations (*e.g.*, mutation of *p53*, absence of *CDKN2A/INK4* function) that are engineered concomitant with *KRAS*^{81–84}. Newer models such as the ELA-CreERT/CAG-lox-*KRAS*^{G12v}, Mist1-*KRAS*, and LSL-*KRAS*^{G12D/p/DPC4^{flox/p} mice have been engineered that mimic human IPMN and MCN^{85,86}. Thus, pancreatic GEMMs represent all the morphological spectrum of pancreatic cancer precursor lesions, as well as the histopathology of precursor lesion progression and its association with inflammation and desmoplasia^{77,81,86,87}.}

Pdx1^{Cre} and P48^{Cre}.LSL-Kras^{G12D} with or without *p53*^{R172H} have been optimized for chemoprevention studies by several laboratories and several agents have been tested in these models. Most of the chemoprevention studies carried out in these models has focused on the intervention of test agents at the stage of early mPanIN progression to mPanIN-3 and invasive adenocarcinoma, providing data that demonstrate improved survival and dose-response effects. Targeting of the epidermal growth factor receptor (EGFR) by Gefitinib or Erlotinib during the mPanIN-2 stage blocks the progression to mPanIN-3 and invasive carcinoma in a dose-dependent manner⁸⁸. Similar efficacious effects were observed with Licofelone, a dual COX-2/5-LOX inhibitor⁸⁹, while the combination of low-doses of Gefitinib and Licofelone completely abolished mPanIN progression to invasive carcinoma⁹⁰. Among other repurposed and Food and Drug Administration (FDA) approved agents that were tested, both statins and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, sulindac, and celecoxib showed effective chemoprevention^{91–97}. In general, most of the well-established chemopreventive agents provided significant efficacy in delaying mPanIN progression to invasive carcinoma, whereas the antidiabetic agent metformin, osteoporosis drugs such as bisphosphonates, and antioxidants had modest chemopreventive efficacy in preventing the mPanIN progression to invasive carcinoma^{98,99}. Interestingly, Minnelide, a natural agent derived from Chinese traditional medicine, showed complete suppression of invasive carcinoma progression and metastasis¹⁰⁰. Thus, existing GEMMs of pancreatic cancer provide important information on the effects of potential chemopreventive agents on precursor lesions and the inhibition of their progression to invasive carcinoma.

David Whitcomb: *What is Currently Being Done for High Risk Patients?*

Some of the agents being used for chemoprevention, for which there is only limited data, are Vitamin D (although the effective dose is unknown), low dose aspirin (mainly for colorectal cancer), and the promotion of a healthy lifestyle, which includes weight control, exercise, less red meat consumption, and more fruit and cruciform vegetables. The development of pancreatic cancer in hereditary pancreatitis starts with bouts of acute pancreatitis, which can last several days and often appears before the age of 10, which then progress to recurrent chronic pancreatitis for months followed by chronic pancreatitis for several years, culminating in pancreatic cancer over several more years to decades which is often first diagnosed in the early 40s. In non-hereditary pancreatitis patients, the risk for the development of pancreatic cancer is elevated in patients with acute or unspecified pancreatitis and chronic pancreatitis. Elevated risk for pancreatic cancer may also occur in other chronic inflammatory disorders.

A major problem in how we deal with chronic diseases in the U.S. is that we are using the wrong disease spending paradigm¹⁰¹. Evidence includes the observation that health care costs are growing rapidly but health outcomes are only improving slowly. A personalized/precision medicine approach will be needed to address complex syndromes which often have multiple etiologies, similar pathologies leading to variable outcomes, and treatment effects with unpredictable effects. One of the problems is that diseases are defined by clinical symptoms and gross pathology with treatments and outcomes based on population statistics. Instead, we need to focus on risk and progression mechanism in individual people rather than associations in populations of people. A mechanistic approach requires using

disease modeling and simulation rather than clinicopathologic classifications. We need guidance for individuals rather than populations. Thus, new approaches are required for new technologies combined with modeling and simulation in individual patients¹⁰².

Further evidence that new approaches are needed come from genome-wide association studies (GWAS). When an unbiased global statistical approach is used for pancreatic cancer, we find that ABO blood types confer some of the highest risk of pancreatic cancer^{102,103}. The potential contributions of common, low frequency, rare, and very rare genetic alleles on effect size was presented along with the potential problems in identifying very rare alleles and combinations of alleles that contribute to pancreatic cancer incidence^{102,104}. The incidence of pancreatic cancer increases with age, peaking in 65 to 74 year olds. This implies that either there are many sequential steps, a few or very few highly specific stochastic events, or both. As the pancreas is protected from most environmental factors the number of stochastic events that occur may be limited compared with other organs¹⁰².

Since pancreatic cancer is an “acquired” disease, this suggests an “event” that must start a pathogenic process¹⁰². As each progressive step likely involves different mechanisms, it follows that different risk factors may be required at different times. Biomarkers should thus be linked to each biologic process (when possible) to monitor disease state, activity, and progression^{105,106}. To date, most of the genetic findings have been discovered by a candidate gene approach¹⁰⁷. The North American Pancreatitis Study 2 (NAPS2) found that 28% of chronic pancreatitis patients exhibit rare genetic mutations associated with risk for pancreatitis. The risk of pancreatic cancer in hereditary pancreatitis occurs 40–50 years after the onset of pancreatitis. The risk of pancreatic cancer in these patients increases with smoking and hereditary pancreatitis families do show clustering; however, some large families do not progress to pancreatic cancer. Of note, *PRSS1* mutation carriers without disease (carriers) do not appear to have an increased risk of pancreatic cancer, suggesting that it is the inflammation, rather than the mutation itself, that is the necessary co-factor for progression to pancreatic cancer. However, the severity of chronic pancreatitis or amount of fibrosis does not correlate with the risk for pancreatic cancer^{108,109}. Thus, inflammation appears to be a trigger but is not sufficient to cause pancreatic cancer in these patients.

Since genetic risk (germline variants) generally remains unchanged throughout life, and if the condition is not congenital, then the effects of the variants will become evident only with organ system stress, organ injury, response to injury or stress, or in the repair/regeneration process. Since the body has two copies of each gene, physiologic reserve, and back-up systems, multiple genetic variants (inherited or acquired) are typically necessary to cause system dysfunction or failure. Our model thus predicts that 1) pancreatitis is necessary, but not sufficient for pancreatic cancer development in this model; 2) toxins that cause DNA damage may also be necessary; 3) pancreatitis likely needs to occur *after* *KRAS* mutations develop in order to activate the *KRAS*; 4) multiple new somatic genetic mutations must be generated in the absence of repair or apoptosis for cancer to develop; 5) preventative strategies may need to include preventing recurrent acute pancreatitis and minimizing the exposure to toxins; and 6) the highest risk patients include those with increased risk for recurrent acute pancreatitis with failed detoxification pathways and defective DNA repair mechanisms.

General Discussion Questions (posed by Jo Ann Rinaudo, NCI)

1. What are the most critical areas of research that may help us identify high-risk pancreatic cancer patients?
2. What possible molecular targets or pathways can be targeted in high-risk individuals?
3. What resources may be needed to identify pancreatic cancer interventions, biomarkers, and cohorts to design early-phase “window-of-opportunity” or “proof-of-concept” trials?

Summary of the General Discussion

- A cohort with a high event rate is needed and whether the IPMN pathway applies to the conventional pancreatic pathway or not, at least it is one where there is a little bit more homogeneity. If an IPMN population is studied, one would have to enrich it; it is still too low of an event. The problem with enrolling the most affected IPMN patients is that some of them probably have subclinical invasive cancer. People with IPMN with lesions may have high-grade dysplasia and some may already have cancer. Since the chemopreventive agent has to match where the patient is in their natural history, the presence of a subclinical invasive cancer could negatively impact a chemoprevention trial. As for familial groups and other patients who are at high risk, the event rates are so low it would be very hard to design a small short study. Those types of trials involve thousands of patients and take a decade.
- The only thing that one can do in a study with a short time frame is show that an intermediate biomarker is affected by the treatment that has been given, and we don't have a validated biomarker. If you are looking at invasive cancer endpoints in a short study, you are actually looking at indolent or prevalent invasive cancer that is already present. So, the absence of an intermediate biomarker makes it hard to do a short study.
- In terms of a window of opportunity/proof-of-concept study, we could look at patients whose risk of progressing to cancer is 25% or more; they may have IPMN lesions and histologically proven PanIN-3 lesions or have five family members and an abnormal EUS. You could learn a lot by doing that study in the near-term. It may not be the perfect study but it is reasonable. Pick the population, put the infrastructure together to do it, and you learn about natural history in a more structured way across multiple institutions, which could really set the foundation for the future as more data emerges on the agent.
- What could we learn from the recent U01 on pancreatitis and diabetes in terms of having multiple agencies fund a study that has many components? Maybe we could apply the same model to study risk stratification of IPMNs; look for biomarkers of IPMNs, and the same

group can also have a smaller study looking at chemoprevention in this same setting, with funding provided by multiple agencies. The Early Detection Research Network (EDRN) is an example of the government providing a framework for multi-institutional collaborative efforts. There are a large group of institutions that are collaborating together to build a multi-institutional cyst fluid repository that also catalogs patient clinical information. This would be a tremendous resource. There are a number of collaborative grants that have resulted from those efforts.

- There is still the potential for a pilot study in chemoprevention. Dr. Peter Allen presented patients who were resected for non-malignant disease and had significant numbers of PanIN-2 lesions. You could enroll patients with IPMNs or pancreatic neuroendocrine tumors that are small and on a chemoprevention targeting agent(s) that are effective at the level of PanIN-2 lesions. One could look at the resected specimen and see whether or not there's less PanIN-2s in those that received the drug vs. those that didn't receive the drug. That's something that could be done that's fairly straightforward; patients with cystic lesions on suspicion for adenocarcinoma can delay pancreatectomy for three months. The issue is accrual—getting those patients in a timely manner—and also what agents or preliminary markers of efficacy we could employ.

Conclusions

1. There was no consensus on an intermediate biomarker that could be measured to assess tumor progression. Many of the panel members had large numbers of patients with IPMNs, for example, but only a small number of these patients progress to invasive cancer. The field needs to develop validated markers that can tell whether cysts are indolent or have the capacity to advance to a more invasive state so they can be treated as such. The same is true of PanIN lesions. PanIN-1 and -2 lesions are widely disseminated among the population but rarely progress to PanIN-3 or further to invasive cancer. Single PanIN lesions are too small to detect, and even if PanIN-3 lesions could be detected it may already be too late because preventive treatment needs to be started with PanIN-2s. There needs to be markers of progression that can indicate whether PanIN-2 lesions will remain indolent or progress to PanIN-3 and then to invasive cancer.
2. There need to be markers to detect PanINs and small IPMNs. One of the issues raised was that it is difficult to detect PanINs or small cysts by imaging methods. PanIN-3s are almost always too small to be detected and are found when they are multifocal based on the apparent scarring that occurs and can be observed. There needs to be molecular markers that can detect PanINs. This is particularly problematic since if they are found in one place in the pancreas they often are found later in other parts of the

- pancreas. There need to be molecular markers that can tag these lesions and then be detected by an imaging method.
3. There needs to be markers of outcome. There are several potential chemoprevention reagents. If a patient is treated with one of these agents, how does one measure their effect?
 4. We have to decide whether to focus on a primary prevention trial that has ramifications for the general population or secondary prevention in a diseased group. These call for different kinds of interventions and different endpoints.
 5. It is apparent that imaging methods are not quite mature enough to provide detailed information on small IPMNs or PanINs. However, an effort is needed to develop methods to extract additional information from current imaging methods using computer based techniques.
 6. The meeting participants recommended the development of an NCI working group to coordinate efforts in these areas and provide the framework regarding what prospective studies should be done and their specifications to try to get at answering these questions. This type of prevention effort will require multicenter studies because of the small groups of patients that can be recruited from individual centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CAF	cancer associated fibroblasts
CEA	carcinoembryonic antigen
CT	computer tomography
CTC	circulating tumor cell
EUS	endoscopic ultrasound
ERCP	endoscopic retrograde cholangiopancreatography
FAP	familial adenomatous polyposis
FPC	familial pancreatic cancer

GEMM	genetically engineered mouse model
GWAS	gene-wide association studies
IPMN	intraductal papillary mucinous neoplasms
LS	Lynch Syndrome
MCNs	cystadenomas/mucinous cystic neoplasms
MRI/MRCP	magnetic resonance imaging/magnetic resonance cholangiopancreatography
NSAID	non-steroidal anti-inflammatory drugs
PanINs	pancreatic intraepithelial neoplasms
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
tPTP	plectin1-targeting protein.

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Table 1

Risk stratification based on the identification of high-risk individuals early in pancreatic disease progression based on current knowledge

Family history (two or more first degree relatives)
Genetic testing
Recent onset diabetes mellitus
Additional factors
Other family cancer history (breast, melanoma)
Demographics: age, race
Exposures: smoking

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