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The Prevention and Genetics of Pancreatic Cancer: A Programmatic Approach

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Abstract

Pancreatic cancer (PC) is typically a fatal disease due to its rapid growth and the lack of early diagnostic techniques. Because approximately 10% of PCs are attributable to a hereditary susceptibility, identifying and studying patients with a family history of PC or known genetic predisposition to PC can improve the prevention, diagnosis, and treatment of PC. A skilled team of study investigators, physicians, genetic counselors, and data managers must work with patients and families to confidentially store and organize data from PC patients and high-risk patients. This data, collected in conjunction with patients' tissue and blood specimens, will contribute to the understanding of the biology, etiology, and epidemiology of PC, and can ultimately improve screening and management for patients with an underlying hereditary predisposition to PC.

Keywords

Pancreatic cancer; Registry; Database; Genetic testing; Cancer prevention; Screening; Surveillance; Hereditary pancreatic cancer; Biorepository; Tissue bank

1. Introduction

Over 200,000 people worldwide die annually of pancreatic cancer (PC) (1). In the United States, pancreatic adenocarcinoma is the fourth leading cause of cancer death in both men and women, resulting in approximately 43,920 new diagnoses and 37,390 deaths in 2012 (2). Prognosis is dismal, with mortality rates that almost equal the incidence, and an overall 5-year survival rate of less than 6% (2– 4).

The etiology of PC remains elusive and our knowledge of its precursors and natural history is preliminary and incomplete. Due to the rapid progression of the disease, patients usually present with symptoms when the tumor is either unresectable or poorly responsive to chemotherapy or radiation (5). The only way to clinically impact disease progression would be through early detection, which to date has been impossible. Currently, no screening strategy is adequately safe, sensitive, or cost effective to be implemented in the general population. Further study is warranted, necessary, and ongoing for improvements in diagnosis, prevention, detection, treatment, and curative options (6).

1.1. Imaging

Various imaging modalities are available for pancreatic cancer detection, including transabdominal ultrasound (US), computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography (EUS). Out of these, EUS seems to be the most

appealing tool for screening because of its high sensitivity and specificity, and low risk of complications. Still, though EUS and MRI technology is improving, our current imaging modalities have neither the sensitivity nor the resolution to sufficiently detect small pancreatic masses or all precursor lesions (3, 6, 7).

1.2. Cancer Syndromes Associated with Pancreatic Cancer

Studies of familial aggregation have shown that approximately 10% of PCs may arise from a hereditary susceptibility (8, 9). For patients with a family history of pancreatic cancer, this percentage translates into a 2.8 to 18-fold increased risk when compared to their control counterparts (10– 14). Known cancer syndromes including hereditary non-polyposis colorectal cancer (HNPCC) or Lynch Syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, Peutz–Jeghers syndrome, and breast ovary cancer syndrome (*BRCA1* and *BRCA2* mutations) (15– 19) account for a small percentage of hereditary PCs. These syndromes result in a lifetime risk of PC ranging from <5 to 40%, and are generally characterized by a clinical phenotype other than PC (15). Hereditary pancreatitis, an autosomal dominant disease which also accounts for a small percentage of hereditary PCs, results in a lifetime risk of PC ranging from 25 to 40% (16). Recently, PALB2 has been recognized as a possible pancreatic cancer susceptibility gene (20). The genetic etiology of other familial pancreatic cancers remains unknown.

1.3. Familial Pancreatic Cancer

At highest risk for PC (up to 50%) are those with a predisposition to pancreatic cancer unrelated to the above familial syndromes (21, 22). Familial pancreatic cancer (FPC) is defined as two or more first-degree relatives with pancreatic ductal adenocarcinoma that have no known associated genetic syndrome (23, 24). Some groups also apply the term FPC for families with PC in three or more relatives of any degree (25, 26). While the genetic basis is yet unknown, segregation analysis suggests that inheritance is via an unidentified, autosomal dominantly inherited gene with reduced penetrance or as a result of interaction between genetic and environmental factors (27, 28).

1.4. Precursor Lesions

Although the natural history of PC still contains many gaps, some progress has been made on a sequential model of progression of morphologically defined preneoplastic lesions (29, 30). Three different noninvasive precursor lesions in particular are known to give rise to invasive carcinoma of the pancreas (31). The first two are mass-forming lesions: intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). IPMNs are classified by varying levels of dysplasia, and arise from either the main pancreatic duct or branch ducts (31, 32). MCNs, on the other hand, do not communicate with the ductal system and are usually accompanied by the presence of unique ovarian-type stroma not found in other pancreatic neoplasms (31, 33). Microscopic duct precursor lesions that may give rise to pancreatic ductal adenocarcinoma (PDAC) have been defined as pancreatic intraepithelial neoplasia (PanIN) (34). Prevalence of PanIN in pancreata has been shown to increase with age and family history of PC (31, 32). These lesions have been further classified into PanIN-1, pancreatic hyperplasia without dysplasia; PanIN-2, variably dysplastic; and PanIN-3, equivalent to carcinoma in situ (31). If this proposed model is correct, and there are identifiable neoplastic lesions in the pancreas with specific morphological and genetic features, there exists an opportunity to profoundly impact the natural history of the disease through the development of safe and accurate screening techniques that will identify these changes before non-resectable carcinoma develops. One possible way of identifying early pancreatic neoplasia is based on the association of multifocal precursor lesions with lobular parenchymal atrophy. If IPMN and PanIN lesions

produce a heterogeneous pattern of atrophy, this atrophy can be detected and quantified on EUS, thereby providing a means of recognizing precursor lesions before they are large enough to be identified through pancreatic imaging (32).

The goal of screening, therefore, is based upon the assumption that if one can identify neoplastic lesions at an early stage, ideally carcinoma in situ or high-grade dysplasia, the patient can be cured or disease prevented. Although this vision has yet to be actualized for pancreatic cancer, it has been demonstrated that patients with lesions <1 cm can be successfully cured (35).

2. Materials

A PC screening and prevention program is most effective at a multidisciplinary tertiary or quaternary medical center. The clinical infrastructure is most comprehensive when comprising experts in internal medicine, gastroenterology, advanced interventional endoscopy, surgery, oncology, basic science, pathology, epidemiology, genetics, radiology, and interventional radiology. In addition to arranging the ideal clinical setting, the research infrastructure must include a database, tumor bank, and blood bank. The large patient volume that accompanies these resources is a requirement for statistical power in any clinical study. Pancreatic cancer patients and high-risk patients are identified for the study in the following ways: outpatient clinics and physician practices, inpatient consultations, patient self-referral, and physician, genetic counselor, or family member referral. Patients are asked to participate in the study by the study investigator, recruitment personnel, or a health care provider.

3. Methods

3.1. Database

Pancreatic cancer patients and high-risk patients must be accrued for enrollment in a comprehensive program registry that will link all clinical patient information to important demographic information.

1. Obtain Institutional Review Board (IRB) approval for a registry database: Because this research deals with human subjects, IRB approval for a registry database is mandatory through an academic or other research institution (see Note 1).
2. Recruit participants: Pancreatic cancer patients and high-risk patients are identified as outlined above in *Materials*. Throughout patient accrual and data collection, physicians, health care providers, study coordinators, and a skilled team of data managers must coordinate to ensure that patient confidentiality is maintained.
3. Collect and store participant data: Patient information will be collected from a questionnaire and other data collection forms, blood specimens, and tissue specimens. Patient information is recorded and stored in a de-identified database. Because data and specimens are de-identified, research utilizing this information is not considered as working with human subjects, and therefore patient consent for this research is not required and information is not provided to subjects (36, 37). This database should include patient health history, family history, clinical treatment and outcomes, surgical specimen information, epidemiologic data, demographics, and any other data collected (such as genetic testing results, diet data, plasma data, etc.). This collection of de-identified, personal patient

[1]Consult your local IRB prior to initiating any registry study. IRBs vary from institution to institution. Therefore, it may be useful to gain insight into your local IRB prior to initiation of study design.

information can be matched with tissue, blood, and other specimens or data and used for future research to elucidate pancreatic cancer etiology and epidemiology.

3.2. Questionnaire

1. Create and administer patient questionnaire: In order to gather detailed patient information, a questionnaire must be designed to accurately collect data on patients' personal health history, family health history, socio-demographic information (i.e., race, sex, religion, employment), epidemiological data (i.e., physical activity, weight, smoking, alcohol and drug histories, diet history) and other desired information, such as patients' attitudes toward cancer genetics, genetic testing, and concerns about PC. Each new participant of the study completes the questionnaire, which will be collected by the research team (see Note 2).
2. Create and implement data collection form: In order to collect information from the patient's medical record, the accruing provider also fills out an intake form, recording important data about the patient's diagnoses, imaging, blood testing, and any treatment of pancreas cancer that the patient has received (i.e., surgery, chemotherapy, and radiation). This form is to be updated annually by the research team. Together, these forms provide a comprehensive view of the patient's health history, both general and in relation to PC.

3.3. Tissue Bank

Collection of both tumor and normal tissue is useful for study in conjunction with the patients' health history. Under no circumstance is tissue obtained solely for the purpose of this study; no additional tissue should be resected beyond that required for surgical purposes.

1. Tumor tissue is useful for analyzing histology characteristics and testing for various genetic and epigenetic abnormalities.
    a. Collect accrued patients' tumor and adjacent normal tissue from surgical procedures.
    b. Request patients' tumor tissue and nearby normal tissue be stored by a pathologist at the institution's Pathology Department when they undergo surgery for any pancreatic tumor resection (see Note 3).
    c. Snap freeze the tissue in liquid nitrogen and store it in −80°C freezers, or store it directly in −80°C freezers.
2. After obtaining consent, request tissue blocks from past surgery performed elsewhere.
3. Tissue from nonsurgical specimens may also be useful for future analysis.
    a. Aspirated fluid or biopsy tissue from endoscopy, including fine-needle aspiration (FNA) specimens; pancreatic secretions and duodenal aspirates; and urine and stool specimens should be obtained, snap frozen in liquid nitrogen, and stored in −80°C freezers.

[2]Questionnaires are often extensive and time consuming for patients. Groups should consider mechanisms for improving return of questionnaires so that the most complete information is available for scientists.
[3]As part of the study, a close collaborative relationship with an expert pancreas pathologist should be developed.

3.4. Blood Bank

Blood bank specimens are to be used for current and future tumor-marker and genetic assessments. The vast majority of subjects will require phlebotomy for other purposes such as pre-endoscopy testing, pre-surgical evaluation, genetic testing when appropriate, or as a part of the clinical evaluation of a problem causing the patient to present to the physician. It is therefore anticipated that only a minority of subjects will require phlebotomy solely for the purpose of these studies.

1. Upon participant entry onto the study, four 4–5 mL tubes of blood are collected. Two tubes should be collected as acid citrate dextrose (ACD) whole blood, one tube as plasma, and one tube as serum.
2. Extract white blood cells from one of the ACD whole blood tubes for immortalization by EBV infection.
3. Extract DNA from the other tube of ACD whole blood, and dissolve it in TE (Tris–EDTA solution). This tube should be stored in a 4°C refrigerator (see Note 4).
4. The serum and plasma tubes are stored in −80°C freezers.

3.5. Risk Stratification

1. Upon presentation, assess each patient for his/her level of risk based upon the number of family members affected and age of onset, and whether the family history is suggestive of a known genetic cancer syndrome. While definitions of risk vary between institutions, at our institution (6):
    a. *Average risk* is de fined as having one family member with PC >55 years old.
    b. *Moderate risk* is de fined as having one or more of the following:
        - ≥2 first-, second-, or third-degree relatives with PC and does not meet criteria for high risk; or
        - 1 first-degree relative with PC <55 years old.
    c. *High risk* is defined as having one or more of the following:
        - Meet the definition of familial pancreatic cancer:
            – ≥3 first-, second-, or third-degree relatives with PC; or
            – ≥2 first-degree relatives with PC; or
            – 1 first- and ≥1 second-degree relatives with PC, 1 at <55 years old.
        - Genetic testing consistent with one of the genetic cancer syndromes associated with PC and at least one family member with PC.

3.6. Approach to Screening

General screening recommendations in patients at high risk of pancreatic cancer are controversial and poorly studied. The following are recommendations based on published

[4]Extracted DNA may be stored in −80°C freezers, but our center has found that repeated thawing and freezing of extracted DNA may cause difficulties with DNA quality. Therefore, we now store the extracted DNA in a −4°C refrigerator.

studies to date (38), as well as our own experience at Columbia University Medical Center (see Note 5).

1. Screen patients as defined under Risk Stratification.
    a. High-risk individuals undergo a baseline EUS and MRI, as well as serum CA19-9, amylase and lipase, and other basic laboratory testing. As a result of these baseline findings, patients undergo alternating EUS and MRI every 6 or 12 months.
    b. Moderate-risk individuals undergo screening with either EUS or MRI, as well as serum CA19-9, amylase and lipase, and other basic laboratory testing.
    c. No screening is recommended for average-risk individuals.

    Our center initiates screening at the age of either 50 or 10 years prior to the earliest age of onset in the family; however, consensus guidelines do not currently exist. For those with Peutz–Jeghers syndrome, screening should begin at 25 years of age.
2. Surveillance should be repeated on an annual basis.
3. Perform an EUS on any patient who presents a concern for a significant pancreatic abnormality. If necessary, FNA or a biopsy can be performed.
4. Consider patient for surgery when either:
    a. There is a high suspicion of malignancy, which may include worrisome changes based on histology, FNA, EUS, or MRI findings.
    b. Main duct IMPN, MCN, or other precancerous abnormalities are detected (39, 40).
    c. Patient meets the Sendai criteria (The 2006 Sendai Consensus Guidelines recommended surgical resection for all suspected branch-duct IMPN greater than 3 cm irrespective of symptoms, and those less than 3 cm with worrisome features; updated guidelines have been recently published (33, 41)).

3.7. Approach to Genetic Testing

1. Genetic testing should be considered when determined appropriate by a physician and genetic counselor.
2. First test the youngest affected family member available, or the proband if the proband has a personal history of cancer (see Note 6).
3. Test for genes known to be associated with pancreatic cancer: *BRCA1/2, STK11/LKB1, PRSS1, p16/CDKN2A, MLH1, MSH2, MSH6, and PMS2* as suggested by the family history (3).

    Consider testing for *PALB2* in families with only pancreas cancer, or in families with pancreas cancer and breast cancer that have normal *BRCA* genetic testing (see Note 7).

[5]A genetics and prevention program can provide the basis for many clinical and translational studies, both at your own institution and in collaboration with others. Consider future studies carefully when designing your IRB, genetics, and prevention programs. Consider consultation with future collaborators prior to sample collection to enable high-quality future studies.

[6]Genetic testing can be a challenging enterprise. Consider using a genetic counselor to help advice patients on risks and benefits of genetic testing.

4. Consider an exception to this approach in the case of suspected *BRCA1/2* mutations in patients of Ashkenazi Jewish descent. For this group, offer multisite *BRCA1/2* testing, even if there is no personal history of cancer.

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[7]Genetic panels for heritable diseases, such as PC, are always being offered by commercial laboratories. Presently, *PALB2* exists in a panel with *BRCA2*.

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