Chapter 6

Hereditary Pancreatic Cancer

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Abstract

Pancreatic cancer is estimated to surpass breast cancer to become the third leading cause of cancer-related death in the USA in 2016. The 5-year overall survival is 7%, and most individuals are diagnosed with advanced disease. Thus, there is a need to improve the early detection of pancreatic cancer in order to detect and improve survival in the same way that mammograms and colonoscopies have improved survival for individuals with breast and colorectal cancer. This chapter discusses the genetics of hereditary pancreatic cancer, the current available screening options, and the use of biomarkers for early detection of pancreatic cancer.

Keywords: pancreatic cancer, genetics, screening, early detection, hereditary, familial

1. Introduction

Pancreatic cancer remains a deadly disease despite decades of research and treatment advances. In 2016 in the USA, it is estimated that pancreatic cancer will become the third leading cause of cancer-related deaths with over 53,000 individuals diagnosed and over 41,000 deaths [1]. Only 9% of newly diagnosed pancreatic cancer is localized and the 5-year overall survival is 7%, which lags behind other solid tumor malignancies [1]. It is estimated that by the year 2030, pancreatic cancer will be the second leading cause of cancer death in the USA [2]. Thus, due to most pancreatic cancers presenting at a later stage with poor overall survival, early detection methods must be implemented to improve treatment outcomes. Pancreatic cancer has been shown through several studies to have a hereditary disposition with estimates ranging from 3 to 16% of newly diagnosed cases [3, 4]. There are several germline mutations that have shown to be at risk for the development of pancreatic cancer, including *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CDKN2A*, *STK11*, *PRSS1*, *MEN1*, *MSH2*, *VHL*, *TP53*, *PALLD*, *EPCAM*, *MLH1*, *MSH6*, *APC*, and *FANCC* [5, 6].

Currently, there are no guidelines for pancreatic cancer screening from the American Cancer Society, National Comprehensive Cancer Network, and the US Preventative Task Force. The International Cancer of the Pancreas Screening (CAPS) Consortium convened in 2011 to examine the best available evidence regarding pancreatic cancer screening to provide guidelines [7]. This book chapter focuses on what constitutes hereditary pancreatic cancer and what risk factors are associated with pancreatic cancer development. We also examine recent literature discussing further methods of early detection of pancreatic cancer.

2. Familial pancreatic cancer genetics

Estimates vary in the literature, but it is recognized that approximately 3–16% of cases of pancreatic cancer have a hereditary component [3, 4, 8, 9]. What constitutes the definition of hereditary pancreatic cancer also varies between known germline mutations with associations with pancreatic cancer to a family history of pancreatic cancer. In individuals with a family history of pancreatic cancer, the risk increases several fold with each first-degree relative (sibling, child, or parent) who is affected. In families with pancreatic cancer, one first-degree relative with pancreatic cancer increased risk by twofold. This risk was increased to nearly threefold if the individual was diagnosed before the age of 60 years [10]. A National Familial Pancreas Tumour Registry (NFPTR) study indicated that the risk of pancreatic cancer increased to 57-fold with three or more affected family members with pancreas cancer [8]. Typically, individuals with hereditary pancreatic cancer also are diagnosed at younger ages (<50 year) compared with those with sporadic pancreatic cancer, which occurs at 61 years of age and older [11]. Also of note is that tobacco use can lead to an increased risk of pancreatic cancer in those individuals at risk due to hereditary pancreatic cancer [11].

There are several genetic syndromes that are related to an increased risk of pancreatic cancer and are summarized in **Table 1**. Hereditary breast and ovarian cancer (HBOC) is associated by germline mutations of *BRCA1* and *BRCA2* [12]. These same mutations also carry a significant risk for the development of pancreatic cancer, with the relative risk varying by at lead two to threefold in those individuals with *BRCA1* and *BRCA2* mutations [13, 14]. The *BRCA1* gene encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability and also acts as a tumor suppressor. The protein is associated with the BRCA1 associated genome surveillance complex (BASC) along with RNA polymerase II with the histone deacetylase complexes. The protein plays a role in transcription along with DNA repair of double-strand breaks and recombination [15]. *BRCA2* encodes for a protein that is also associated with double-strand break repair and homologous recombination. It is also associated with multiple proteins, including RAD51 and PALB2 [16]. *PALB2* (partner and localizer of BRCA2) has also recently been recognized as a significant germline mutation associated with HBOC and involved in the development for pancreatic cancer [17]. The roles of these mutations in the pathogenesis of pancreatic cancer has not always been clear in preclinical animal models, but it is agreed that they contribute to defective DNA repair that leads to accumulation of damaged DNA and genomic instability that would lead to pancreatic cancer development [18].

Syndrome	Gene (s) involved	Clinical features
Hereditary breast and ovarian cancer (HBOC)	*BRCA1*, *BRCA2*, *PALB2*	Breast cancer, ovarian cancer, male breast cancer, uveal melanoma, stomach cancer, biliary cancer, endometrial cancer.
Ataxia-telangiectasia	*ATM*	Cerebellar ataxia, telangiectasia of the conjunctiva and skin, immunodeficiency, leukemia.
Lynch	*MLH1*, *MSH2*, *MSH6*, *PMS2*	Colorectal cancer, endometrial cancer, ovarian cancer, stomach cancer, small bowel cancer, transitional cell cancer, glioma, and sebaceous neoplasms.
Peut-Jeghers (PJS)	*STK11*	Mucocutaneous pigmentation, hamartomatous polyps; colorectal, stomach, small bowel, testicular, breast, cervical, and ovarian cancer
Familial adenomatous polyposis (FAP)	*APC*, *MUTYH*	Colorectal cancer, desmoid tumors, medulloblastomas, osteomas, fibromas, supernumerary teeth, gastric polyps
Familial atypical mole and multiple melanoma (FAMMM)	*CDNK2A*	Melanoma, CNS malignancies, Acute Lymphoblastic leukemia.
Familial pancreatitis	*PRSS1*, *CFTR*, *SPINK1*, *CASR*, *CTRC*, *CPA1*	Pancreatitis, cystic fibrosis, diabetes
Li-Fraumeni	*TP53*	Sarcomas, breast cancer, Gliomas, Choroid plexus carcinomas, and adrenocortical carcinomas
Fanconi's anemia	*FANCC*, *FANCG*	Aplastic anemia, bone marrow failure, acute myeloid leukemia, myelodysplatic syndrome

Table 1. Inherited syndromes associated with increased risk of pancreatic cancer.

Other DNA repair mechanism-based genes implicated in familial pancreatic cancer include the gene *ATM*, whose product works with several proteins involved in DNA damage and subsequently the cell cycle [19]. The gene *ATM* is more commonly known in relation to Ataxia-telangiectasia which is manifested by progressive cerebellar ataxia, oculomotor apraxia, telangiectasia of the conjunctiva and skin, immunodeficiency, sensitivity to ionizing radiation, and an increase rate of malignancies such as leukemia. In one series of 166 familial pancreatic cancer probands, 2.4% carried deleterious mutations [19]. Lynch syndrome, which is an autosomal dominant disorder caused by a germline mutation in one of either *MLH1*, *MSH2*, *MSH6*, or *PMS2*. The genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* function as DNA mismatch repair genes. Lynch syndrome can also occur because of loss of expression of *MSH2* due to deletion in the *EPCAM* gene [20]. Typical affected family members of lynch have an increased risk of colon cancer but are at risk for several other malignancies, including pancreatic cancer [21]. The risk of pancreatic cancer in families with Lynch syndrome has been reported to be as high as an 8.6-fold increase with a cumulative risk of 3.7% by age of 70 years [22]. Another familial syndrome associated with colon cancer is familial adenomatous polyposis (FAP). This also follows an autosomal dominant pattern of inheritance in the *APC* gene. *APC* is a tumor

suppressor gene that is involved in the Wnt signaling pathway along with pathways associated with migration and adhesion, transcription, and apoptosis. Pancreatic cancer has been reported to have a relative risk of 4.46 in families with familial adenomatous polyposis [23]. A variant of FAP, attenuated familial adenomatous polyposis (AFAP) is characterized by mutations in the *MUTYH* gene [24]. To date there is no reported linkage with this gene with pancreatic cancer development although due to its involvement in DNA damage repair an association with pancreatic cancer risk may be discovered.

Peutz-Jegher syndrome (PJS) is another autosomal dominant syndrome that leads to risks in several malignancies. It is characterized clinically by multiple hamartomatous polyps in the gastrointestinal tract and mucocutaneous pigmentation. Individuals with PJS are affected by mutations in *STK11* gene which is a serine threonine kinase tumor suppressor gene. Colon, stomach, small bowel, ovarian, breast, cervical, and testicular cancer risk is increased, as is pancreatic cancer The risk of pancreatic cancer in some studies has indicated as high as a 26% risk in those with *STK11* mutations for pancreatic cancer development by the age of 70 with a relative risk of 76 [25].

Familial atypical mole and multiple melanoma (FAMMM) syndrome is yet another autosomal dominant disorder that is characterized by family members with multiple nevi along with cutaneous and ocular melanomas. This disorder involves mutations in the *p16* gene or *CDNK2* gene which also can lead to pancreatic cancer. The risk of pancreatic cancer development by the age of 75 has been reported to be between 17 and 25% [26, 27]. In some studies, there has been reported to be a 13- to 22-fold increase of pancreatic cancer [27]. CDKN2A is a tumor suppressor involved in inducing cell cycle arrest in the G1 and G2 phase. What is interesting about the *CDKN2A* gene is that somatic mutations or other alterations occur in 90% of individuals with pancreatic cancer making it an important step in tumor promotion in pancreatic cancer [28].

Chronic or recurrent acute pancreatitis also has a hereditary component that has become associated with pancreatic cancer development [29]. In families with hereditary pancreatitis, the risk for pancreatic cancer increases substantially past the age of 50, with the risk being 10% by the age of 50, increasing to 19% by the age of 60, and then to 54% by the age of 75 years in one study [30]. In individuals who smoke with hereditary pancreatitis, the risk of pancreatic cancer increase by twofold if they are current or former smokers and pancreatic cancer in these individuals occurs 20 years earlier [31]. The genetics of hereditary pancreatitis is complex. Germline mutations in the serine protease 1 gene (*PRSS1*) follows an autosomal dominant pattern for hereditary pancreatitis. The gene function of this enzyme functions as a protectant against trypsin. Trypsin is a digestive enzyme secreted by the pancreas into the duodenum and control of its activity is through several proteins including PRSS1, serine protease inhibitor Kazal 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsinogen C (CTRC), and calcium-sensing receptor (CASR) [32]. The repeated exposure of trypsin and resulting pancreatitis has been shown preclinically to induce pancreatic fibrosis and inflammation [33]. Biallelic alterations in the aforementioned gene *SPINK1*, leads to an autosomal recessive pattern of chronic pancreatitis [34]. *SPINK1* encodes a pancreatic secretory trypsin inhibitor and is regulated as an acute phase reactant being expressed during the

inflammatory process acting as a feedback inhibitor in trypsin [34]. *CFTR* follows an even more complex genetic pattern with regards to hereditary pancreatitis [35]. CFTR functions as an ion channel involved in the transport of chloride and thiocyanate and is associated with cystic fibrosis, a condition manifested by pancreatic insufficiency, failure to thrive, sinus disease, and respiratory disease [36]. Homozygotes mutations of the *CFTR* gene lead to severe chronic pancreatitis but compound heterozygote mutations may also lead to chronic pancreatitis [37]. Homozygous mutations carry a risk of 40–80-fold for chronic pancreatitis over the general population [37]. Individuals who carry only one allelic mutation of the *CFTR* gene still are at an increased risk of chronic pancreatitis three- to fourfold over the general population. Those individuals with heterozygous *CFTR* mutations typically have coexisting germline mutations in either *SPINK1* or *CTRC* [38]. The *CTRC* gene carries a risk for chronic pancreatitis but usually in conjunction in individuals with mutations in either *CFTR* or *SPINK1* [39]. *CTRC* encodes the enzyme Chymotrypsin C that helps degrades trypsin. Other genes associated with recurrent acute and chronic pancreatitis have also been discovered. *CLDN2* encodes a protein that function in tight junction and is involved in ion and water transportation. Mutations in this gene have been associated with chronic pancreatitis particularly in those individuals who consume alcohol. It has recently been described to be involved in pancreatic acinar cells [40]. And finally, the gene *CPA1* encodes a pancreatic digestive enzyme whose mutations have been found to be involved in early onset of chronic pancreatitis. The mutation appears to be involved in endoplasmic reticulum stress as opposed to direct trypsin activity in regards to the development of chronic pancreatitis [41].

There are other syndromes that do not have nearly as strong evidence as the aforementioned syndromes for pancreatic cancer risk, but studies have indicated there are associations. Li-Fraumeni syndrome is an autosomal dominant disorder that is a result of germline mutations in the tumor protein p53 gene (*TP53*) [42]. *TP53* is a tumor suppressor gene that has a major role in regulating the cell cycle in response to DNA damage. In its absence, cells containing damaged DNA survive and proliferate leading to malignant transformation. Typical malignancies at risk with germline mutations in *TP53* include osteosarcomas, rhabdomyosarcomas, breast cancer, gliomas, and adrenocortical carcinomas [42]. However, in a study of 24 families with confirmed *TP53* germline mutations, the risk of pancreatic cancer was 7.3-fold compared to the general population [43]. Fanconi anemia is an autosomal recessive or X-linked disorder that results in congenital malformations along with pancytopenia and macrocytic anemia and is characterized by germline mutations in the *FANC* family of genes [44]. These groups of genes are involved in DNA repair and interact with the BRCA pathway. Mutations in the *FANCC* and *FANCG* genes have been reported in families that have developed young onset (less than 55 years of age) pancreatic cancer [45, 46].

As genetic sequencing become more cost effective for the greater population there will likely be more genes discovered in relation to the risk of pancreatic cancer. Traditional sequencing of gene discovery may uncover additional germline mutations along with single nucleotide poylmorphisms (SNPs). Epigenetic sequencing analysis may also unveil methylated promoters that place an individual at risk for the development of pancreatic cancer. An example of whole genomic sequencing identifying new risks in the human genome came from a study

examining over 1890 individuals with pancreatic cancer and compared with 2654 controls that showed an association between a locus on 9q34 and pancreatic cancer through the SNP rs505922 [47]. This SNP maps to the first intron of the ABO blood group gene which leads credence to prior epidemiologic evidence suggesting that individuals with blood group O may have a lower risk of pancreatic cancer than those with groups A or B [47].

3. Other risk factors for pancreatic cancer development

Other risk factors exist for the development of pancreatic cancer and may be associated with changes in the human genome based upon enhanced environmental susceptibility with specific germline alterations. What is currently known is that obesity plays a risk for the development of pancreatic cancer. Two longitudinal US cohort studies, the Health Professionals Follow-up study and the Nurses' Health Study, had decades of follow-up through questionnaires which examined the risk of Body Mass Index (BMI), height, and level of physical activity. Individuals with a BMI of at least 30 kg/m^2 had an elevated risk of pancreatic cancer compared with those with a BMI less than 23 kg/m^2 with a relative risk of 1.72. Height was also associated with an increased pancreatic cancer risk of 1.81 RR when comparing the tallest category (equal to or greater than 185.4 cm in men, greater than 167.6 cm in women) to the shortest category (less than or equal to 172.7 cm in men, less than 157.5 cm in women). In individuals with moderate physical activity defined as equal to or greater than 11.0 MET hours per week in men and equal to or greater than 10.8 MET hours per week in women, the risk of pancreatic cancer was reduced by 59% in men and 48% in women [48]. The "Western" dietary pattern of high intake of saturated fats and smoked or processed meats has also been shown to influence the risk of pancreatic cancer development. In a 7-year prospective study, those that had the highest quintile of intake of processed meat had a 68% increased risk compared with those in the lowest quintile. Higher intake pork and red meat compared with the lowest quintiles were also associated with a 50% risk of pancreatic cancer [49]. A meta-analysis of 11 prospective studies published in 2012 confirmed that processed meat consumption was associated with an increased risk of pancreatic cancer in men but not in women. The relative risk in men was 1.29 [50]. Other social risk factors that are modifiable include tobacco use and alcohol use, particularly heavy alcohol use since it contributes to the development of pancreatitis. Heavy alcohol use is defined as having at least nine drinks per day [51]. Tobacco use leads to a 2.2-fold increased risk of developing pancreatic cancer and cessation must take place for 20 years prior to returning to the risk of nonsmokers [52]. Of note is that exposure of second-hand smoke confers an odds ratio of 1.21 relative to those individuals with no exposure [53]. The risk increases in active smokers by cigarette pack-years.

Diabetes has been recognized more and more as a tremendous risk factor for pancreatic cancer development. Due to one of the functions of the pancreas in regulating glucose metabolism, diabetes is a common presenting finding for pancreatic cancer. In one dose-response meta-analysis of prospective observational studies, it was shown that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in the rate of pancreatic cancer [54]. This roughly translates to around a 0.35% change in the Hemoglobin A1C (HgbA1C). In

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another meta-analysis examining 44 studies of diabetes and pancreatic cancer risk, the duration of diabetes was associated with increased risk. For individuals with longer duration of diabetes, the relative risk slowly decreased, with RR being 1.64 for having diabetes for at least 2 years, then RR of 1.58 for diabetes at least five years, and 1.50 RR for having diabetes for at least 10 years [55]. In a nested case-control study within the Health Improvement Network in the UK, new onset of type 2 diabetes was associated with an estimate odds ratio (OR) of 2.16 of pancreatic cancer [56].

Other environmental risk factors include Hepatitis B virus infection and *Helicobacter pylori* infection. Both have been seen in studies and likely warrant further analysis. In a meta-analysis of nine studies involving 3033 patients, the risk of *H. pylori* infection was associated with an OR of 1.47 of developing pancreatic cancer. When broken down into regions such as East Asia the OR goes up to 2.01, but in North America it is 1.17 [57]. The association of hepatitis B virus has also been seen albeit in a single institution study of 476 pancreatic cancer patients and 879 healthy controls. The adjusted odds ratio (AOR) of hepatitis B exposure and pancreatic cancer was 2.5 in anti-Hepatitis B core antigen positive (HBc) patients, 2.3 in anti-HBc positive/anti-Hepatitis B surface antigen (HBsAg) positive patients, and the AOR was 4 for anti-HBc positive/antiHBs negative patients [58]. A cohort of over 66,000 men and women were followed in the Vitamins and Lifestyle study from 2000 to 2008. During follow up, 151 individuals developed pancreatic cancer. Magnesium intake was studied, and for every 100 mg/day decrement in magnesium intake, there was a 24% increase in the incidence of pancreatic cancer through multi-variate analysis that included age, gender, body mass index, and nonsteroidal anti-inflammatory drug (NSAID) use. Thus, magnesium intake may be beneficial for primary prevention of pancreatic cancer [59]. The etiology of why magnesium would be protective for pancreatic cancer is not completely clear. There have been associations with magnesium and the improvement in insulin sensitivity. Deficiency in magnesium may also be associated with free radical formation that leads to DNA damage and cancer development [60], and magnesium may act as a scavenger of harmful chemicals [61].

The microbiome is a burgeoning field involving the study of the microbial flora in humans and its effect on health. Human flora in the mucocutaneous surfaces are composed of a variety of aerobic and anaerobic bacteria. The human microbiome is altered by several environmental factors along with host hygiene such as alcohol use, periodontitis, and the use of antibiotics. The microbiome may play a greater role in inflammation and the eventual development of several malignancies, including pancreatic cancer [62]. A study examining the microbiome by oral wash samples from 361 individuals who developed pancreatic cancer and comparing it to 371 matched controls showed the presence of two species of bacteria, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* associated with an increased risk of pancreatic cancer [63]. The presence of *P. gingivalis* in oral wash samples was associated with a 59% increased risk for pancreatic cancer and the presence of *A. actinomycetemcomitans* was associated with a 119% increased risk. These findings do not establish a true causal link but are intriguing and warrant greater investigation as influencing the microbiome may have a dramatic in pancreatic cancer prevention.

4. Methods of early detection of pancreatic cancer

Because pancreatic cancer carries a poor prognosis, identifying those individuals at risk for developing it is vital due to a phenomenon called anticipation. Anticipation in genetics is defined as when a genetic disorder is passed on the next generation, the symptoms of the genetic disorder become apparent at an earlier age. This is true in several familial forms of cancer such as breast or colorectal and influences when an individual is recommend screening modalities such as mammogram or colonoscopy. In a large study examining 1223 individuals from 106 families with familial pancreatic cancer, anticipation was noted. For individuals affected with pancreatic cancer, the median age of death from pancreatic cancer was 70 years old in generation one, 64 years old in generation two, and 49 years old in generation three [64].

In 2010, the International Cancer of the Pancreas Screening (CAPS) consortium was formed to help organize global pancreatic screening [7]. The consortium was composed of 50 experts from 10 countries in the fields of epidemiology, genetics, gastroenterology, radiology, oncology, surgery, and pathology. This group was composed of physicians, research scientists, and genetic counselors from a wide variety of practice settings including community-based practices and academic centers. The consensus on who should be offered screening was based upon best available evidence. For individuals with three or more blood relatives with pancreatic cancer, with at least one affected first-degree relative (FDR) should be considered for screening. FDR denotes either a parent, brother, sister, or child. Those with at least two affected FDRs should be considered for screening. And finally those with two affected blood relatives with pancreatic cancer with at least one FDR should be considered. For those individuals with only a young onset pancreatic cancer relative (not an FDR), there was no consensus reached on offering screening. In regards to mutation carriers, those with Peutz-Jeghers regardless of family history should be considered for screening. For *BRCA2* mutation carriers with one or more affected FDR with pancreatic cancer and those with two or more affected family members (even without a FDR) should be considered for screening. For *PALB2* mutation carriers with one or more affected FDR should be considered for screening. For individuals with *p16* germline mutations with one or more affected FDR with pancreatic cancer should be considered for screening. For individuals with Lynch syndrome with one or more affected FDR with pancreatic cancer should be considered for screening. The age to initiate screening was not agreed upon nor the age to end screening. The consensus regarding screening modalities was utilizing endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) [7]. Computed tomography (CT) of the abdomen has the disadvantage of utilizing radiation as opposed to MRI/MRCP's reliance of magnetic fields. Furthermore, in a screening program utilizing either CT, MRI, or EUS, CT scans were inferior in detecting pancreatic lesions. CT scans detected pancreatic abnormalities in 11% of the individuals compared with 33.3% for MRI and 42.6% for EUS [65]. As always, the risks of these modalities must be considered, particularly with EUS. Regarding the routine follow up per the CAPS consortium, a 12-month interval was recommended but no consensus on what tests to repeat. Surgical intervention for pancreatic lesions was also recommended to be considered after multidisciplinary assessment, preferably within research studies [7].

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There are a handful of published studies on screening for pancreatic cancer. One study published in 2010 from Columbia University Medical Center/NewYork Presbyterian Hospital utilized a screening program similar to the recommendations put forth from the CAPS consortium. In this study, individuals with a family history of pancreatic cancer were allowed to enroll in a prospective screening study and were placed into three risk groups: average, moderate, or high risk. The individuals in average risk were those with one family member with pancreas cancer diagnosed over the age of 55 years old. Individuals with moderate risk were defined as those with two first-, second-, or third-degree relatives with pancreatic cancer or those with one first-degree relative with pancreatic cancer less than 55 years of age. A second-degree relative denotes an aunt, uncle, grandparent, grandchild, niece, nephew, or half-brother or half-sister. A third-degree relative denotes a great grandparent, great grandchildren, and first cousins. Individuals were defined as high risk for pancreatic cancer if there were three or more first-, second-, or third-degree relatives with pancreatic cancer; two or more first-degree relatives with pancreatic cancer; one first-degree relative and one second-degree relative if one was diagnosed at 55 years or younger, and any genetic syndrome associated with pancreatic cancer such as BRCA, Peutz-Jeghers Syndrome, Lynch, Familial Melanoma, or hereditary pancreatitis. Depending upon the individual's risk, they were offered basic blood testing (average risk) or blood testing with MRI (moderate risk) or blood testing, EUS, and MRI (high risk). In these asymptomatic individuals, pancreatic cancer was detected in two of them- one resectable and one stage IV pancreatic cancer. Four patients has intraductal mucinous neoplasms (IPMN) lesions, two individuals were diagnosed with ovarian cancer, one individual with retroperitoneal carcinoid, and one with papillary carcinoma of the thyroid [4]. All told, 18% of the 51 asymptomatic individuals in the program were found to have a preneoplastic or neoplastic lesion. In a follow-up report on their website, 7 of the 29 individuals that have continued screening have also been found to have abnormalities of the pancreas [66]. In another study enrolling 411 asymptomatic individuals performed through a multi-institutional collaboration in Europe, surveillance was offered through individuals at risk for pancreatic cancer [67]. Individuals with a confirmed *CDKN2A* mutation or with a personal history of melanoma and a known mutation in the family were eligible along with individuals from families with two or three first-degree relative with pancreatic cancer. All individuals were offered MRI/MRCP along with EUS every third year of screening. For individuals with *CDNK2A* mutations, 13 (7.3%) developed pancreatic cancer. The resection rate in those individuals was 75% and the 5-year survival was 24%. In the familial pancreatic cancer cohort, 13 individuals (6.1%) underwent a surgical resection, but only four had high-risk lesions. In a cohort of 10 individuals with *BRCA1/2* or *PALB2* mutation, one individual (3.8%) developed pancreatic cancer [67]. Various screening studies have been published throughout the past several years examining several at risk-populations. Routine screening for pancreatic cancer in all healthy individuals currently is not recommended.

Biomarkers for pancreatic cancer continue to be developed. As mentioned previously, the occurrence of diabetes typically precedes pancreatic cancer and bears monitoring in those individuals at risk for pancreatic cancer development. Carbohydrate antigen aka cancer antigen 19–9 (CA 19–9) is the most common pancreatic cancer serum biomarker. However, this biomarker's sensitivity and specificity are not high as several benign conditions involving the

gastro-biliary system can cause its elevation [68]. Furthermore, in individuals with negative Lewis phenotype, the CA 19–9 is not elevated, even in the setting of widely metastatic pancreatic cancer. Therefore, the development of newer biomarkers is of interest for pancreatic cancer and those at risk for developing it. A study originating from MD Anderson and Dr. Raghu Kalluri's lab looked at exosomes, which are lipid-bilayer-enclosed extracellular vesicles that contain protein and nucleic acids. The identification of cell surface proteoglycan, glypican-1 (GPC1) is specifically enriched in cancer cells, particularly pancreatic cancer. The assay itself simply uses a small amount of peripheral blood. In comparing individuals without cancer and those with pancreatic cancer, the expression of GPC1 was always elevated in individuals with pancreatic cancer. In a study examining the GPC1 levels in response to surgical resection of pancreatic cancer, individuals who had a greater decrease of detectable GPC1 levels than those that did not correlated to an improved overall survival [69]. Thus, GPC1 may be a biomarker of interest for individuals at risk for pancreatic cancer. Another study identified elevated plasma levels of branched-chain amino acids (BCAAs) are associated with an increased risk of future pancreatic cancer diagnosis. The study examined cases of pancreatic cancer with matched controls from four prospective cohort studies with blood collected at least 2 years before cancer diagnosis with the median time between blood collection and pancreatic cancer diagnosis being 8.7 years. Several metabolites were analysed, and the BCAAs isoleucine, leucine, and valine stood out as an increased risk of greater than twofold for pancreatic cancer development [70]. Circulating BCAAs are elevated in obese individuals and those with insulin resistance [71]. These findings also suggest that muscle protein loss happens much earlier than anticipated in pancreatic cancer, thus contributing further to the debilitating nature of this cancer. Other noninvasive serum approaches include the use of circulating tumor DNA (ctDNA). In a study of patients who underwent resection of their primary pancreatic tumor, the detection of ctDNA preceded the presence of measurable recurrent pancreatic cancer on CT by 9.9 months [72]. Other clinical studies have examined the use of urinary KRAS in advanced cancers requiring very small copy numbers of the KRAS ctDNA [73]. The implications of this and other work suggests that noninvasive testing is improving for detecting pancreatic cancer and may be a consideration for clinical trial design in cohorts of those individuals at risk of the developing pancreatic cancer.

5. Future directions

Pancreatic cancer remains a difficult cancer to diagnose and treat. The identification of individuals who are at risk for pancreatic cancer is important for several reasons. The first significant benefit is for the individual to be aware of their risk and to undergo a surveillance program for the early detection of pancreatic cancer. This program should be compromised of multi-disciplinary panel composed of oncologists, gastroenterologists, radiologists, pathologists, and genetic counsellors. The benefit of early detection for an individual at high risk is for improved survival for pancreatic cancer. Through remarkable work from Johns Hopkins and Dr. Christine Iacobuzio-Donahue's lab from autopsy series, pancreatic cancer appears to take about 20 years from the first mutated cell to clinical presentation and metastasis [74]. This

provides a window of opportunity in regards to early detection of the disease and a chance to change the natural course of pancreatic cancer in an individual. The other benefits lie in identifying individuals at risk for pancreatic cancer development and offering these individuals opportunities to participate in clinical trials examining biomarkers—through either serum, urine, or imaging or a combination. The improvement in the overall 5-year survival in breast cancer was not born out of improved treatment for metastatic breast cancer, but through the use of mammography, increased awareness of the cancer, and optimal management of localized disease through a multi-modality approach. In an editorial by Hait and Levine, they argued that the main focus by oncologists has been in treating tumors that are genetically complex [75]. Their argument focuses on examining premalignant lesions and the likelihood of dealing with less genetically complex lesions with treatment. One example of this approach is the use of imatinib, a Bcr-abl inhibitor that is incredibly effective against chronic myelogenous leukemia (CML). The effectiveness of this drug is measured by complete haematological response (CHR). During the chronic phase of CML where the cancer genome is relatively simple, the CHR is 95% for imatinib. As the tumor becomes more genetically complex through disease progression of accelerated phase and then myeloid blast crisis, the CHR falls to 38% and 7%, respectively [75]. This is what oncologists deal with pancreatic cancer, a cancer that has likely metastasized by the time of clinical presentation, hence the low response rates of current therapies.

The oppurtunity to detect pancreatic cancer early through better assays may also allow for intervention. For instance, an individual without confirmed histological confirmation by way of EUS with an elevated biomarker that is highly sensitive and specific to pancreatic cancer may consider watchful waiting or treatment. The treatment may include agents such as metformin, a biguanide which reduces weight and decreases fasting plasma insulin concentrations by enhancing insulin sensitivity via activation of 5'-AMP-activated protein kinase (AMPK) [76]. Metformin has also shown benefit in preclinical models in pancreatic cancer [77]. In a study of individuals who underwent resection for pancreatic cancer, metformin use was associated with an improved survival [78]. The use of immunotherapeutic agents that have so far been met with disappointment in treating advanced pancreatic cancer, may have significantly improved outcomes in premalignant or early pancreatic cancer. Another example of early intervention may be through the use of RANK ligand inhibitors that are available commercially such as Denosumab (Xgeva, Prolia). In a three-dimensional organoid breast cancer model from women that have *BRCA1* mutation and pre-neoplastic legions, the inhibition of RANKL substantially curtailed tumorogenesis [79]. The possibility of offering a drug like Denosumab which is administered subcutaneously and has relative few side effects as opposed to offering a women with *BRCA1* mutation risk reducing mastectomy or bilateral oophorectomy particularly at a young age would likely be appealing for most individuals.

Costs of screening protocols in individuals at risk for pancreatic cancer development have been examined and appears to be cost-effective [80]. Utilizing early detection programs through several institutions may define better the risk factors for pancreatic cancer along with initiating clinical trials for earlier intervention. The potential benefits of identifying and improving survival in individuals with pancreatic cancer is tremendous. By examining those at high risk

for developing the disease, the possibility of developing a more widespread early detection tool for pancreatic cancer in the vein as mammograms may save countless lives in the future.

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