PANCREATIC CANCER RISK PERCEPTION AND WORRY IN FAMILIAL HIGH-RISK PATIENTS UNDERGOING ENDOSCOPIC ULTRASOUND FOR SURVEILLANCE

by

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BS, Cell and Molecular Biology; California State University Northridge; 2008

Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2012

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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Pancreatic cancer is a devastating disease with a five-year survival rate of 5.6%. Approximately 5 – 10% of cancer diagnoses are due to a hereditary predisposition. While some cancer syndromes have been shown to increase the risk for pancreatic cancer above the population risk of ~2%, a gene for familial pancreatic cancer has not been identified. In either of these situations, surveillance for high-risk individuals has not been well established as compared to other more common cancers associated with hereditary cancer syndromes. The goal of this study is to identify familial individuals' top motivation for attending the high-risk pancreas clinic, and for those individuals who elect endoscopic ultrasound, assess if their feelings about their cancer risk and level of worry change after the procedure.

For this study, a high-risk, unaffected population was recruited, along with a comparison group of individuals referred for endoscopic ultrasound due to a pancreatic abnormality. Using the Health Belief Model as a framework, participants were asked to complete two validated questionnaires pertaining to their cancer risk perception and level of worry about pancreatic cancer. The first questionnaire was completed before the endoscopic ultrasound, and the second questionnaire was sent home with the participant after the procedure for completion.

Data analysis revealed both similarities and differences in the two cohorts. Both populations showed similar trends in the benefits of the endoscopic ultrasound and the fear of the

procedure due to a potential negative outcome. Family history and familial support demonstrated the largest difference in trend values between the case and comparison cohorts

This study has public health importance because of the serious consequences of pancreatic cancer. High-risk individuals are looking for surveillance options to improve the early detection of pancreatic cancer, and to date, there is not an established surveillance protocol. As more research is done, a better understanding of the psychosocial impact of surveillance in this population can be better understood.

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PREFACE

First and foremost, I would like to thank all the participants for being so open about such a sensitive subject. Having the opportunity to discuss their feelings and experiences is something I will take with me into my professional career.

I would like to thank my family for their support. Without their constant cheering from 3,000 miles away, I would not be the person I am today.

I would especially like to recognize my thesis committee for their guidance throughout this process. I would also like to thank my classmates for their constant support during our two years together at the University of Pittsburgh.

1.0 INTRODUCTION

Approximately 5 – 10% of pancreatic cancers are due to an inherited predisposition. Individuals have an increased risk for developing pancreatic cancer based on the number of affected family members with pancreatic cancer and other cancers in the family medical history, as well as the presence of a known germline mutation. Germline mutations are heritable changes in the DNA sequence that can be passed from generation to generation. Current technologies, including MRI and endoscopic ultrasound, are used for surveillance of the pancreas in this high-risk, healthy patient population.

Little is known about the effectiveness of surveillance for pancreatic cancer using endoscopic ultrasound. It is unclear how well the procedure detects early stage pancreatic cancer in this high-risk population, when cancer may be more treatable. As part of the informed consent process, the limitations of the testing should be explained to all patients having the procedure. Symptomatic patients and those with a pancreatic cancer diagnosis may not see the limitations of endoscopic ultrasound as a barrier for the test. This may be due to the fact that endoscopic ultrasound is being used as a diagnostic test rather than as a surveillance tool.

To explore the cancer risk perception in two populations, the Health Belief Model was used as a framework for this study. These two populations were considered either high-risk cases or comparisons. Cases are defined as those asymptomatic individuals with a family history of pancreatic cancer who undergo endoscopic ultrasound as a surveillance tool. Comparisons are

categorized as those individuals who are symptomatic patients who are using endoscopic ultrasound as a diagnostic tool. The aim of this study is to identify familial individuals' top motivation for attending the high-risk pancreas clinic. In addition, for those high-risk individuals who elect to have the endoscopic ultrasound, the study examined their perceptions of cancer risk and cancer worry before and after the endoscopic procedure.

2.0 BACKGROUND

2.1 THE PANCREAS

The pancreas is a vital organ located in the abdomen, behind the stomach. It contains two different types of glands: exocrine and endocrine. About 95% of the pancreas is made up of exocrine cells (American Cancer Society). These cells create enzymes required for digestion. These enzymes flow through small ducts that eventually merge with the pancreatic duct. A small percentage (about 5%) of pancreatic cells are endocrine cells and are arranged in small clusters known as *islets of Langerhans* (American Cancer Society). These cells are responsible for releasing important hormones like insulin and glucagon into the blood stream to control the amount of sugar present. Diabetes can result from the inability of these cells to produce insulin. The pancreas also has an extensive duct system. The main duct connects the pancreas to the common bile duct at the ampulla of Vater and transports the digestive enzymes into the duodenum.

Exocrine and endocrine cells form completely different types of tumors. Endocrine tumors are quite rare and are termed neuroendocrine tumors. They are typically named for the hormone-making cell they start in (e.g. insulinomas, glucagonomas, gastrinomas). Exocrine tumors are the most common type found in the pancreas. Adenocarcinomas tend to start in the glands of the pancreas, while less common tumors arise from the pancreatic ducts. The deep

location in the abdomen is not conducive to palpable tumors. These tumors are the main focus of this study.

2.2 GENERAL FACTS OF PANCREATIC CANCER

Pancreatic cancer is the fourth most common cancer in both men and women in the United States (Lewis et al., 2009). The incidence of pancreatic cancer in African Americans is higher than in Caucasians. Pancreatic cancer is seen in 13.5 per 100,000 Caucasian males and 10.5 per 100,000 Caucasian females (Klein, 2012). In the African American population, the risk to males is 17.1 per 100,000 and 14.8 per 100,000 in females. According to the American Cancer Society, the lifetime risk to develop pancreatic cancer in the general population is approximately one in 71 or 1.41%. Approximately 80% of pancreatic cancers have already metastasized when diagnosed (Klein, 2012). These diagnoses are usually made after the patient has become symptomatic due to the metastasis. The most common presenting symptoms in metastatic patients are epigastric pain, weight loss, and obstructive jaundice (Brand et al., 2007). Overall five-year survival rate is only 5.6% (Stoita et al., 2011). Once a diagnosis has been made, the median survival rate is around six months (Stoita et al., 2011).

2.2.1 Types of pancreatic cancer

The most common type of pancreatic cancer is adenocarcinomas of the pancreas. It accounts for greater than 90% of diagnoses (Brand et al., 2007). As of now, there are three known precursor lesions to pancreatic cancer. Intraductal papillary mucinous neoplasm (IPMN) is the most likely

precursor to turn malignant. Approximately 70% of main duct IPMN and 25% of branch duct IPMN are found to be malignant (Stoita et al., 2011). The second type of precursor lesion is known as the pancreatic intra-epithelial (PanIN). This type of lesion is the most common type found. The third type of precursor lesion is a mucinous cystic neoplasia (MCN). PanINs and IPMNs are the most common lesions seen in patients with a strong family history of pancreatic cancer (Shi et al., 2009). Larger lesions, including main duct IPMNs and MCNs, can be detected by CT and MRI. Smaller pancreatic changes, like branch duct IPMNs and chronic pancreatitis, are best detected using an endoscopic ultrasound (Stoita et al., 2011).

2.2.2 Risk Factors

The most important risk factor for pancreatic cancer is age. More than 80% of individuals diagnosed with pancreatic cancer are between the ages of 60 and 80 (Brand et al., 2007). Almost all patients are over the age of 45, with the average age of diagnosis being 72 (American Cancer Society). Risk factors for pancreatic cancer have been separated into three subgroups of relative risk. Relative risk is defined as the ratio of the incidence of a disease among individuals with a given risk factor (e.g. a genetic mutation, lifestyle choice, environmental exposure) versus the incidence of a disease among individuals without a given risk factor (i.e. the general population). These groups are based on the degree to which they increase the risk for developing pancreatic cancer over that of the general population. Those risk factors that increase the cancer risk by less than five-fold over the general population are placed in the “low” group. Those risk factors that increase the cancer risk between five and ten-fold are in the “moderate” group. The “high” group are those factors that increase the risk by greater than ten-fold.

2.2.2.1 Low (<5-fold)

Those risk factors in the low category increase the risk for pancreatic cancer less than five-fold above the general population (Brand et al., 2007). Individuals who are male, of African American decent, or of Ashkenazi Jewish descent have a two-fold increased risk to develop pancreatic cancer. The most significant lifestyle risk factor is cigarette smoking. Active smoking has been shown to carry a 1.77-fold increased risk for pancreatic cancer (Lynch et al., 2008). Former smokers have a 1.2-fold increased risk (Klein, 2012). Fifteen years after smoking cessation, individuals have a similar risk to those who have never smoked (Lynch et al., 2008). Diabetes mellitus has also been shown to increase the risk for pancreatic cancer. The overall risk is a 1.94-fold increase over the general population (Ben et al., 2010). This risk seems to be the highest within the first year of diabetes mellitus diagnosis.

Increased body mass also seems to be a risk factor for pancreatic cancer. Normal body mass index (BMI) is between 18.9 and 24.9. Individuals with a BMI greater than 35 have a 1.19-fold increased risk to develop pancreatic cancer (Berrington de Gonzalez et al., 2003). Excessive alcohol consumption is another lifestyle risk factor. Consumption of six or more drinks per day has a 1.46-fold increased risk for pancreatic cancer (Klein, 2012). Other risk factors in this group include an *Helicobacter pylori* infection, a history of any cancer in a first-degree relative, hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, individuals with a *BRCA1* mutation, and a history of pancreatic cancer in one first-degree relative (Brand et al., 2007). First-degree relatives are those family members that share 50% of the genetic material with the proband. This includes parents, children, and siblings.

2.2.2.2 Moderate (5 – 10-fold)

An example of a moderate risk factor for pancreatic cancer is the Mendelian condition cystic fibrosis (CF). CF is an autosomal recessive condition characterized by abnormal transport of sodium and chloride across the epithelial layer. This leads to thick, viscous secretions primarily found in the lungs, pancreas, and GI tract. One report indicates a 2.6-fold increased risk for pancreatic cancer, while another report shows a 32-fold increased risk, with a confidence interval from 4.8 to 205 (Brand et al., 2007). Depending on the mutation in the *CFTR* gene, the amount of pancreatic and GI involvement may differ.

Chronic pancreatitis also falls into the moderate risk category. Chronic pancreatitis is associated with repeated inflammation of the pancreas. This long-standing inflammation affects the structure and function of the pancreas. There is also conflicting data about the true risk associated with this condition. One report shows between a 16.5 and 19-fold increased risk for pancreatic cancer, while another showed only a two-fold increase (Brand et al., 2007). Because of the variability of both of these conditions, they have been placed in the moderate group (Brand et al., 2007). Other factors in this group include a family history of pancreatic cancer in two first-degree relatives and *BRCA2* mutation carriers.

2.2.2.3 High (>10-fold)

A majority of risk factors in the high category are those with a hereditary predisposition to pancreatic cancer. These include FAMMM kindreds with an identified *p16* mutation and at least one case of pancreatic cancer in a first- or second-degree relative, Peutz-Jeghers syndrome, hereditary pancreatitis, and a family history of three or more first, second, or third-degree relatives with pancreatic cancer (Brand et al., 2007). For the purposes of this paper, kindred is defined as a group of related individuals. New evidence supports placing *BRCA1/2* families with

at least one case of pancreatic cancer in first or second-degree relatives into this high-risk group (Brand et al., 2007).

2.2.2.4 Gene-Environment Interactions

Studies have suggested that there is a direct link between genetic and environmental interactions that carry an increased risk for pancreatic cancer. For this section, environmental risk factors also include those that are considered lifestyle risk factors. It has been shown that there may be an additive risk when combining genetic and environmental risk factors in a single individual. One example of this is the combination of hereditary pancreatitis and cigarette smoking. Hereditary pancreatitis alone holds a risk of 53-fold greater than the general population (Lowenfels et al., 1997). But when an individual is also a smoker, his risk is elevated to 154-fold above the general population (Lowenfels et al., 2001). It is thought that the combination of progressive glandular damage from the pancreatitis and the chemicals from cigarette usage leads to this significantly increased risk for pancreatic cancer (Lowenfels et al., 2001). Additionally, there also seems to be a correlation with the onset of pancreatic cancer in these individuals. Non-smokers with hereditary pancreatitis seem to have an average age of onset around 70 years of age, while those individuals who are smokers see an age of onset around 50 (Matsubayashi, 2011). It is important to educate individuals at increased risk for pancreatic cancer due to a hereditary predisposition about the increased risk associated with environmental factors. Smoking, obesity, and diabetes mellitus are all environmental factors that are shown to carry an increased risk due to a gene-environment interaction.

2.3 HEREDITARY CANCER SYNDROMES

Cancer is a disease known throughout the world. It is estimated that one in three individuals will develop cancer at some point in his/her lifetime (American Cancer Society). It is estimated that approximately 5 – 10% of all diagnoses result from an inherited gene mutation. There are specific features that suggest an inherited predisposition to cancer: multiple cancer diagnoses in a family with some under the age of 50, multiple generations with a related cancer diagnosis, individuals with multiple primary tumors, unusual or rare tumors, and/or families from a specific ethnic background known to have an increased carrier frequency (Lindor & Greene, 1998). Several hereditary cancer syndromes are associated with an increased risk for pancreatic cancer. Much like the overall cancer statistics, it is believed that approximately 5 – 10% of all pancreatic cancer diagnosed result from an inherited gene mutation (Matsubayashi, 2011). The increased risk for pancreatic cancer spans anywhere between 5 – 40%, depending on the specific syndrome and/or the number of family members affected (Maheu et al., 2010).

2.3.1 Peutz-Jeghers Syndrome (PJS)

Peutz-Jeghers syndrome is an autosomal dominant cancer syndrome associated with multiple gastrointestinal hamartomatous polyps and pigmented spots on the lips and buccal mucosa. It is caused by mutations in the *STK11* gene, a serine threonine kinase gene that acts as a tumor suppressor. The prevalence is approximately one in 8,300 – 280,000 (Matsubayashi, 2011). A clinical diagnosis can be made in an individual with one of the following features: two or more histologically confirmed PJS polyps, any number of PJS polyps detected in one individual who has a family history of PJS in a close relative, characteristic mucocutaneous pigmentation in an

individual who has a family history of PJS in a close relative, or any number of PJS polyps in an individual who has characteristic mucocutaneous pigmentation (NCCN). Individuals diagnosed with PJS have an overall lifetime cancer risk of 70% (van Lier et al., 2010). The overall cancer risk is also associated with 60% of deaths in the PJS population (Boardman et al., 1998). Studies have shown that the pancreatic cancer risk is 132-fold above the general population in these families, with a lifetime risk of 11 – 32% (van Lier et al., 2010). These individuals also have an age of onset around 40, earlier than other hereditary syndromes (Matsubayashi, 2011).

2.3.2 Hereditary Pancreatitis

Hereditary pancreatitis is an inherited form of chronic pancreatitis that is characterized by repeated attacks of acute pancreatitis, or inflammation of the pancreas. These repeated attacks start early in life and lead to long-term exocrine and endocrine damage. The natural history and prevalence of hereditary pancreatitis has not been well documented (Rebours et al., 2009). A majority of these families have mutations in the cationic trypsinogen gene *PRSS1*, which results in the autosomal dominant form. Mutations in the serine protease inhibitor gene, *SPINK1*, cause the autosomal recessive form. Both types of mutations lead to early activation of the pancreatic enzymes that begin to digest the organ rather than waiting to activate in the duodenum. Regardless of the gene mutation, individuals have a 53-fold increased risk to develop pancreatic cancer (Lowenfels et al., 1997). This condition also carries a lifetime risk for pancreatic cancer between 30 and 40% by age 70 (Ulrich et al., 2001), with this risk even higher among smokers. This diagnosis can occur 20 years earlier than in patients who do not smoke (Klapman et al., 2008).

2.3.3 Familial Atypical Multiple Mole Melanoma (FAMMM)

Familial Atypical Multiple Mole Melanoma is an autosomal dominant cancer syndrome characterized by multiple dysplastic nevi and melanoma. It is caused by mutations in *p16/CDKN2A*, a tumor suppressor gene. It is estimated that 5 – 7% of individuals with melanoma are from genetically high-risk families, though exact carrier frequencies are not known (Greene, 1997). A clinical diagnosis can be made in a family with one or more first- or second-degree relatives with malignant melanoma or an individual with a total body nevi count of greater than 50 including some of which are clinically atypical (NCCN). The two most common malignancies in FAMMM kindreds are melanoma and pancreatic cancer. Other associated cancers include lung, breast, and sarcoma. Studies have shown that the risk for pancreatic cancer in FAMMM kindreds is a 38-fold increase (Matsubayashi, 2011). In familial melanoma families without a *p16* mutation, the risk is estimated to be between a 13 and 22-fold increase (Lynch et al., 2008).

2.3.4 Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC or Lynch Syndrome)

Lynch syndrome is an autosomal dominant cancer syndrome associated with right-sided colon cancers and other abdominal malignancies. It is caused by mutations in the mismatch repair pathway. Lynch syndrome may account for 6 – 10% of all colon cancer diagnoses (Vasen et al., 1996). A clinical diagnosis can be made, in some cases, by the Amsterdam II criteria. This includes three individuals with a Lynch syndrome-related cancer, with one relative being a first-degree relative of the other two; two successive generations are affected; and one diagnosis must

occur under the age of 50 (NCCN). Of note, Lynch syndrome-related cancers include endometrial, ovarian, small bowel, stomach, bile duct, and urinary tract. Individuals from Lynch syndrome kindreds have an 8.6-fold increased risk for pancreatic cancer and a lifetime risk of 3.86% (Kastrinos et al., 2009). Interestingly, Lynch syndrome families with microsatellite instability are more prone to be diagnosed with medullary pancreatic cancer. It is also believed that the prognosis is better in individuals with microsatellite unstable pancreatic cancers (Matsubayashi, 2011).

2.3.5 Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

Hereditary breast and ovarian cancer syndrome is an autosomal dominant cancer syndrome primarily associated with an increased risk for breast and ovarian cancer, with additional cancer risks as well. It is caused by mutations in the tumor suppressor genes *BRCA1* and *BRCA2*. Carrier frequency in the general population is believed to be one in 500, although Founder populations (i.e. individuals of Easter European [Ashkenazi] Jewish ethnicity) may have a carrier frequency as high as one in 40 (Struewing et al., 1997). Clinical characteristics of HBOC include: the presence of two or more breast and ovarian cancer diagnoses; early age of onset (defined as before age 50); generation-to-generation transmission; individuals with multiple primary tumors (e.g. bilateral breast cancer, breast and ovarian cancer); unusual tumors (e.g. ovarian cancer, pancreatic cancer); and Ashkenazi Jewish ethnic background (NCCN). Studies have shown a 3.5-fold increased risk for pancreatic cancer in individuals with a *BRCA2* mutation (The Breast Cancer Linkage Consortium, 1999). With this association, the presence of pancreatic cancer in an "HBOC-looking" family is a good predictor of a *BRCA2* mutation (Phelan et al., 1996). It is believed that *BRCA2* mutations are the most common gene

responsible for familial aggregations of pancreatic cancer (Matsubayashi, 2011). There are conflicting reports about the risk for individuals with a *BRCA1* mutation. Some studies have shown a 2.26-fold increased risk for pancreatic cancer, while others have shown no significant increased risk when compared to the general population (Thompson et al., 2002; Ferrone et al., 2009).

2.3.6 Familial Adenomatous Polyposis Syndrome (FAP)

Familial adenomatous polyposis syndrome is an autosomal dominant cancer syndrome associated with a lifetime risk for colon cancer reaching 100%. It is caused by mutations in the tumor suppressor gene *APC*, with 25% to 33% of cases being *de novo*. The incidence of FAP is thought to be one in 6,000 – 13,000 (Rhodes et al., 1992). A clinical diagnosis can be made in an individual with greater than 100 adenomas in the colon or an individual with fewer than 100 adenomas and a family history of FAP (NCCN). While the true risk associated with FAP is for colon and extra-colonic cancers, these individuals are also at a slightly increased risk for pancreatic cancer. *APC* mutations are associated with a relative risk of 4.5 for pancreatic cancer (Giardiello et al., 1993). However, it is thought that invasive duodenal cancer, a tumor strongly associated with FAP, may be mistaken as pancreatic cancer (Larghi et al., 2009). Because of this, it may be an overestimation of the pancreatic cancer risk. Aside from the adenocarcinoma of the pancreas, individuals are also at risk for pancreatoblastoma due to bi-allelic inactivation of *APC* (Matsubayashi, 2011).

2.3.7 Familial Pancreatic Cancer Syndrome (FPC)

Familial pancreatic cancer syndrome is presumed to be an autosomal dominant cancer syndrome associated with a predisposition for developing pancreatic cancer. Unlike the other hereditary cancer syndromes, the genetic basis of FPC has not been identified. This syndrome is defined as a family with at least two first-degree relatives with pancreatic cancer (Stoita et al., 2011). Additionally, this diagnosis should be made only when all other cancer syndromes have been evaluated and excluded (Lindor & Greene, 1998). Cancer risks in families with FPC have been identified based on the number of affected family members. For individuals with two affected first-degree relatives, the relative risk for pancreatic cancer is 6.4%, with a lifetime risk of eight to twelve percent (Klein et al., 2004). Individuals who have three affected first-degree relatives have a relative risk for pancreatic cancer of 32% and a lifetime risk of 16 – 32% (Tersmette et al., 2001).

When evaluating a family for one of the established hereditary cancer syndromes, age of onset for pancreatic cancer is not typically taken into account because of its rarity. However, age of onset is important when a family is being considered for a FPC diagnosis. The risk for pancreatic cancer is higher in FPC kindreds when age of onset is younger than the average seen in other hereditary cancer syndromes (Stoita et al., 2011). This is likely due to the fact that anticipation has been seen in FPC kindreds. Anticipation is where the symptoms of a genetic disorder become apparent at an earlier age as it is passed on to the next generation. In many cases, there is also an increase in the severity of the disease. In 2006, McFaul et al. observed an age of onset difference of six years between generations. It is important to note that anticipation is family specific. The progress of individuals in one family towards an earlier onset should not

be relevant to the progression in another family, unless there is a common ancestor (McFaul et al., 2006).

2.4 SURVEILLANCE FOR PANCREATIC CANCER

At this time, no established guidelines exist for screening or surveillance for pancreatic cancer to assist health care professionals (Brand, 2011). Routine screening for pancreatic cancer is not recommended for the general population. However, a select subset of individuals may warrant further surveillance (Lewis et al., 2009). It is important to note the difference between cancer screening and cancer surveillance. Screening techniques are available to the general population as a means to detect early stage cancer. There are a few cancers with a technique that has been proven to be effective in the general population. These include mammography for breast cancer, colonoscopy for colon cancer, pap smears for cervical cancer, and the prostate-specific antigen (PSA) blood test for prostate cancer (American Cancer Society). Surveillance techniques are those that are only made available to particular high-risk populations (American Cancer Society).

The overall goal of surveillance is to detect precursor lesions or early pancreatic cancer when it may be at its most treatable stage (Stoita et al., 2011). Premalignant lesions and small pancreatic cancers tend to be asymptomatic. It is believed that stage I tumors less than two centimeters have a much better survival rate (58% at five years) when compared with stage IIb (17% at five years) (Stoita et al., 2011).

2.4.1 High-Risk Populations

Who should be included in surveillance for pancreatic cancer has been widely debated. For other common types of cancer, like breast and colon, surveillance algorithms have been created to capture appropriate populations (NCCN). These same algorithms have not been extensively studied for the pancreatic cancer patient population due to the relatively small numbers (Larghi et al., 2009). In 2003, experts gathered at the Fourth International Symposium of Inherited Diseases of the Pancreas. With the lack of evidence for a solid algorithm, these experts created the consensus practice recommendations for pancreatic cancer surveillance (Brand et al., 2007).

Surveillance is considered appropriate for individuals who have a greater than 10-fold increased risk for pancreatic cancer (Brand et al., 2007). This group includes FAMMM, hereditary pancreatitis, PJS, and three or more first-, second-, or third-degree relatives with pancreatic cancer. In families with a *BRCA1* or *BRCA2* mutation, surveillance may be considered when there is a first- or second-degree relative with pancreatic cancer (Brand et al., 2007). Other individuals may be considered for surveillance if they do not meet the criteria above, but may have compounding environmental risk factors that have increased their pancreatic cancer risk (Lewis et al., 2009). There remains a question for individuals who fall into the 5 – 10-fold increased risk category. It is suggested that until an algorithm of cost-effectiveness vs. benefits to the individual is created for pancreatic cancer surveillance, surveillance may be used until further studies can establish a risk threshold (Larghi et al., 2009).

2.4.2 Surveillance Options: Benefits and Limitations

Experts have not only debated who should have surveillance, but also the type of surveillance to offer and when to start surveillance. Several surveillance options are available, and a variety of protocols have been proposed, but experts have not been able to reach a consensus on which protocol should be used as the standard of care for high-risk populations. Endoscopic ultrasound (EUS) remains the best first-line imaging technique for pancreatic cancer (Lewis et al., 2009). The body and tail of the pancreas lie directly posterior to the stomach. This position lends itself to a highly detailed endosonographic evaluation and the ability to biopsy any portion of the pancreas (Folkers et al., 2011). An important point to make with high-risk individuals is that, in their case, EUS is being used as a surveillance tool. The procedure was originally created as a diagnostic tool for confirmation of pancreatic abnormalities. So while it is the same procedure being performed, it is being used in two different circumstances.

Although EUS is considered the gold standard at some institutions, it does have some limitations. The procedure requires sedation, because of the invasive scope used (Canto et al., 2004). If the lesion is not within centimeters of the luminal GI tract, it may not be accessible by EUS. Other limitations of EUS can be seen in individuals with pancreatitis. Searching for small abnormalities in a pancreas with severe pancreatic parenchyma could be difficult (Larghi et al., 2009). EUS is also a subjective test, and different readings may be seen between even the most experienced sonographers. There are cases where resection was ordered on a mass that ended up being a benign lesion (Larghi et al., 2009). This has happened more in individuals who have witnessed the ravages of terminal pancreatic cancer in their relatives and pushed for resection out of fear (Larghi et al., 2009).

Other imaging techniques have also been suggested, including MRI, CT, and endoscopic retrograde cholangiopancreatography (ERCP). CT can identify only lesions greater than two centimeters (Stoita et al., 2011). Overall, EUS and MRI can detect pancreatic lesions better than CT (Canto et al., 2012). None of these imaging studies has been shown to detect small tumors in asymptomatic patients (Brand et al., 2007; Poley et al., 2009). ERCP does have a three to five percent risk for procedure-related acute pancreatitis. Biomarker tests have also been suggested. CA 19-9 was originally used as a management tool for individuals with pancreatic cancer (Goonetilleke et al., 2007). However in the asymptomatic population, CA 19-9 is neither specific nor sensitive enough to be used as a sole surveillance tool (Stoita et al., 2011). At this point in time, EUS may currently be the most promising imaging modality for surveillance of these high-risk individuals (Larghi et al., 2009). The procedure has a sensitivity of 84% and a specificity of 92% (Stoita et al., 2011).

It has been suggested that certain steps be taken in order to improve early detection strategies (Brand, 2011):

1. Better define the high-risk populations where the positive predictive value of advanced precursor lesions warrants close monitoring with costly and invasive testing. A positive predictive value is the proportion of individuals with a positive test result who are correctly diagnosed.
2. Better understand the pathogenesis of pancreatic cancers.
3. Create methods that can reliably detect advanced precursor lesions (PanIN) or predict when IPMNs will progress to adenocarcinomas.

4. Determine whether early detection strategies may appear to improve survival by identifying pancreatic cancer earlier in the disease course, when it may be more treatable.

The ultimate goal of surveillance is early detection that will ultimately lead to surgical resection. Surgery is the only potentially curative treatment for pancreatic cancer. The prognosis is most favorable with indicators that include a tumor size of less than three centimeters, the ability to excise with negative resection margins, negative nodal involvement, and the absence of vessel invasion (Yoshizawa et al., 2011). It has also been found that the quality of life is highest amongst patients who had a pancreaticoduodenectomy, also known as the Whipple procedure (Yoshizawa et al., 2011). Overall, surveillance for high-risk individuals has a yield of approximately 8%, with the highest yield seen in high-risk patients over the age of 65 (Ludwig et al., 2011).

2.4.3 Implementing Surveillance

Wide variability is seen with the onset of pancreatic cancer when comparing hereditary cancer syndromes, so when to start surveillance has also been debated. The earliest onset is associated with PJS syndrome. These families are more likely to develop associated cancers at a younger age, so surveillance generally begins between 25 and 30 years of age (van Lier et al., 2010). FPC families tend to begin surveillance around the age of 40, or 10 years before the earliest diagnosis in the family. But anticipation has also been noted in these families, where this regimen may not capture some family members (Larghi et al., 2009).

Current recommendations, like those for FPC, suggest starting surveillance at age 40, or ten years before the earliest diagnosis in all high-risk families excluding PJS. However, these

recommendations do not take into account coexisting risk factors, like smoking or diabetes mellitus. In FPC and hereditary pancreatitis families, smoking can hasten the age of onset by one to two decades (Larghi et al., 2009).

In asymptomatic individuals, it has been recommended that surveillance use a yearly follow-up plan. If an abnormal finding is seen, surveillance may be increased to every three to six or three to twelve months (Matsubayashi, 2011). Slow growing tumors, such as IPMN, may require increased surveillance every three to six months.

2.4.4 Genetic Counseling

Cancer risk assessment in conjunction with genetic counseling is the process of identifying and counseling individuals who are at an increased risk for developing cancer based on pedigree analysis, genetic risk models, biochemical tests, physical characteristics (when necessary), and imaging, to identify potential hereditary cancer syndromes in a family (Riley et al., 2011). Several studies have looked at the impact of genetic counseling for breast cancer from the patient's perceptive (Braithwaite et al., 2004; Meiser et al., 2002). The overall theme of these studies is that genetic counseling for hereditary breast cancer increases accuracy of cancer risk perception and decreases overall anxiety in the high-risk population.

2.4.4.1 Genetic Counseling for Pancreatic cancer

The effectiveness of genetic counseling has come into question for diseases where the causative gene has not been identified, as with hereditary pancreatic cancer (Axilbund et al., 2005). Effectiveness of genetic counseling is defined by Axilbund *et al.*, as how well the counseling increases risk perceptions and decreases generalized anxiety. While other cancer syndromes

have been identified that carry an increased risk for pancreatic cancer, a single gene has not been identified that would predispose to familial pancreatic cancer.

Early data show that genetic counseling may be effective in preventing an increase in psychosocial distress (Maheu et al., 2010). It is recommended that a complete family history be taken to identify any family members with the potential to carry a gene of one of the known hereditary cancer syndromes (Brand et al., 2007). In the absence of a known hereditary syndrome, information should be given to families regarding potential cancer risks, given the family history. Genetic counselors play a key role in communicating potential clinical research protocols that may include new surveillance options (Axilbund et al., 2005). Although this information may be lacking when compared to other, well-studied cancer syndromes, individuals tend to appreciate the information provided during a genetic counseling session (Axilbund et al., 2005).

2.4.4.2 UPMC High-Risk Pancreas Clinic

The University of Pittsburgh Medical Center (UPMC) High-Risk Pancreas Clinic is under the direction of Dr. Randall Brand and his genetic counselor, Sheila Solomon, MS, CGC. The goal of the clinic is provide specific risk assessment for pancreatic cancer and prevention and surveillance options to individuals.

All patients are seen at the clinic through some type of referral. Most often, these referrals come from a patient's primary care physician, oncologist, genetic counselor, or other family member. Once a referral has been received, patients are scheduled for a clinic visit, which is held twice a week at UPMC Shadyside.

Patients are first seen by the genetic counselor for the intake. This includes gathering the patient's medical and family history, explaining potential genes that could be involved, the

function of genes and chromosomes, and cancer risks. The structure of the genetic counseling session is similar to a general cancer genetics counseling session, with particular emphasis on hereditary syndromes of the pancreas. An assessment of the family is done to identify if a hereditary predisposition to pancreatic cancer may exist. Once the counseling portion is completed, Dr. Brand speaks to the patients from the medical approach. He discusses whether or not he is suspicious for a hereditary predisposition to pancreatic cancer. If so, potential genetic testing is discussed if an identified gene exists for the syndrome in question. Lastly, he discusses the current status of prevention and surveillance. At the time of recruitment, the current prevention recommendations included smoking cessation, a healthy diet, weight loss if necessary, regular exercise, and 2000IU Vitamin D (Stolzenberg-Solomon et al., 2010). Dr. Brand also discusses endoscopic ultrasound. He explains the way the outpatient procedure works, what the patients can expect before and after the procedure, and the benefits and limitations. At this point, the patient would decide whether or not to proceed with scheduling the procedure. Lastly, Dr. Brand's research coordinators invite the patients to participate in his research studies, including the PAGER study.

2.4.5 Emotional Impact of Surveillance and Genetic Counseling

Numerous studies (Bjorvatn et al., 2007; Keogh et al., 2011; Price et al., 2007) have looked at risk perception and the level of worry in the more common hereditary cancer syndromes, like hereditary breast and ovarian cancer syndrome and hereditary non-polyposis colorectal cancer syndrome. Bjorvatn et al. conducted a study that explored how patients felt about their risk for developing cancer and their level of worry. Their study included patients with a family history of a first- or second-degree relative with breast cancer, colon cancer, or a combination of the

two. The study concluded that the patients' perceived risk decreased after genetic counseling (Bjorvatn et al., 2007). It was thought that this decrease could be due to a preconceived idea of their risk before counseling based on their personal experiences. This study also asked patients to recall information about the surveillance options that were available to them. Twenty-seven percent of participants in this study gave incorrect answers when asked about inclusion in a surveillance program (Bjorvatn et al., 2007). This may have been due to the fact that surveillance was not a main focus of the counseling session, which is different from the UPMC High-Risk Pancreas Clinic. Overall, this study showed that the level of worry was reduced after one genetic counseling session (Bjorvatn et al., 2007).

Keogh et al. conducted a study in 2011 aimed at describing the risk perception and screening behavior of women who were at an increased, but unexplained familial risk for breast cancer. The study included women with at least one first- or second-degree relative with breast cancer under the age of 50. Women who had a *BRCA* mutation in their family were excluded. During analysis, researchers found that perceived risk could not be separated from their emotional response to their risk. Through interviews with participants, risk perception was defined as a layered concept. It included their understanding of heredity, risk factors, genetics and popular discourses (Keogh et al., 2011). These women felt a sense of the social expectations about how they should interpret and manage their risk. They felt they had to justify their thoughts that may have been inconsistent with their actions, including surveillance (Keogh et al., 2011).

A third study, conducted by Price et al., aimed to identify predictors of cancer worry in high-risk, unaffected women in breast cancer families. Participants of this study included unaffected women with a significant family history of breast or ovarian cancer, or a documented

BRCA mutation in the family. Overall, the study showed that the level of worry in these women was generally low, despite reporting their perceived risk of developing breast cancer as 50% (Price et al., 2007). A woman's worry about breast cancer is influenced by a range of factors including risk perception, and that her personal experiences have an independent affect on worry, asides from her own sense of risk (Price et al., 2007). The strongest predictor of worry was general anxiety and may be due to the woman's personal experience with familial breast cancer.

Little is known about the effect of surveillance and genetic counseling on the well-being of those at high risk for pancreatic cancer (Hart et al., 2011). As shown above, extensive studies have been done on the effective outcome of genetic counseling in the more common high-risk cancer syndromes, like breast, ovarian, and colon (Braithwaite et al., 2004; Ellen et al., 2008; Keller et al., 2008; Meiser et al., 2002). Unfortunately, these same studies have not been conducted in large numbers for individuals at risk for pancreatic cancer. It has been found that pancreatic lesions are more common in the high-risk populations (Canto et al., 2012). The issue then becomes which ones warrant surgical resection and which ones can be followed by surveillance. Experts anticipate that there will be a positive impact on a patient's level of cancer worry once surveillance and prevention strategies are shown to be effective (Maheu et al., 2010).

Studies have been conducted on the value of genetic counseling for FPC kindreds. Overall, individuals felt that genetic counseling was valuable, despite the lack of genetic testing for a causative gene (Axilbund et al., 2005). However, in this same study patients reported frustration with the genetic counseling session because of the lack of current knowledge. Studies have also evaluated individuals' perceived cancer risk and how genetic counseling impacted their perception of risk. Overall, patients at all cancer risk levels tended to overestimate their pancreatic cancer risk, and their view was not greatly influenced by genetic

counseling (Axilbund et al., 2005). This may be due to younger individuals with a strong family history of pancreatic cancer who have watched multiple family members fighting the disease (Maheu et al., 2010). This may also be due to the fact that there are no pancreatic cancer survivors in the family. This is in contrast to other hereditary cancer syndromes, where there may be family members who have survived their cancer diagnosis.

2.5 HEALTH BELIEF MODEL

The Health Belief Model (HBM) is a theoretical construct that has served as a framework in studies to explain asymptomatic individuals' uptake of cancer surveillance (Lewis et al., 2009). It is one of the oldest and most widely used conceptual frameworks of health behavior (Guvenc et al., 2010). Initially introduced by Hochbaum et al. in the 1950s, the model focuses on four main concepts: susceptibility, seriousness, benefits, and barriers. Perceived susceptibility is an individual's perception of his likelihood of experiencing a condition that would adversely affect his own health. Perceived seriousness is a person's interpretation of the degree of intensity of a particular disease. Perceived benefits are a person's assessment of the positive consequences of adopting the behavior. Perceived barriers are the individual's assessment of the influences that facilitate or discourage the promoted behavior

The framework states that an individual's health behavior will be the result of the personal cost-benefit analysis based on these concepts. Studies have been performed using HBM, looking at individuals' willingness to have surveillance for pancreatic cancer. In 2009, Lewis et al. found that the individuals who were most motivated to have surveillance were those that had the greatest overall perceived risk for all types of cancers (e.g. those in the breast cancer

group who had a personal history and those in the pancreatic cancer sub-groups). Overall, the HBM has generated research regarding behaviors for health maintenance or prevention of disease in the healthy population (Champion, 1984).

The HBM has been revised by Victoria Champion to measure the constructs as it relates to breast cancer and surveillance behavior (Champion, 1984, 1985, 1993, 1999). A questionnaire was created to test the main constructs for validity and reliability. These scales were then termed Champion's Health Belief Model (CHBM) scales (Champion & Scott, 1997). The goal of these scales was to create an instrument that would be both reliable and valid and could be consistently used (Champion, 1993). Champion created these scales by measuring the uptake of breast examinations in women. Her study found that there is a point at which individuals will pursue particular cancer surveillance. This is most apparent when an individual perceives his risk as high and perceives the barriers as low (Lewis et al., 2009). Since then, the construct of her model has been modified to evaluate the cancer surveillance uptake for different cancer screenings, for use in other countries, and with different ethnicities. She has also evaluated the mammography uptake in African American women (Champion et al., 2008). Other researchers have translated the validated questionnaire for use in assessing the uptake of breast cancer surveillance in non-English speaking countries (Gozum et al., 2004; Medina-Shepherd et al., 2010; Taymoori et al., 2009). In all of these studies, the CHBM scales have been validated. In addition to its use in other languages, the CHBM scales have also been validated in the study of other cancer surveillances. The uptake of colonoscopies and pap smears has been studied using the CHBM scales (Guvenc et al., 2011; Mitchell et al., 2011). All validated studies have shown this same relationship between uptake of a particular surveillance method when the perceived risk is high and perceived barriers are low. In addition, these studies all show when individuals

believe the surveillance method is beneficial, they have less fear about the procedure itself. While the CHBM scales have been used in other surveillance procedures, this is its first known use for pancreatic cancer surveillance and its psychosocial impact.

3.0 AIM OF STUDY

The aim of this study is to identify individuals' top motivation for attending the high-risk pancreas clinic. In addition, for those high-risk individuals who elect to have the endoscopic ultrasound, the study will examine their perceptions of cancer risk and cancer worry before and after the endoscopic procedure.

4.0 METHODS AND PROCEDURES

This study was implemented as a modification to the current protocol, The Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study – A prospective cohort study of patients at risk or having pancreatic disease. The addition of the questionnaires was reviewed and approved by the University of Pittsburgh Institutional Review Board (MOD07030072-28), which can be seen in Appendix A.

4.1 PARTICIPANTS

Study participants were recruited through their involvement in the PAGER study. Once enrolled in PAGER, individuals were approached about their participation in this study. Patients were seen at either the UPMC Shadyside or the UPMC Presbyterian Gastrointestinal (GI) Labs for EUS. Three separate groups were formed depending on their status: initial visits, return visits, and comparisons. Patients in the initial visit and return visit groups were considered the case cohort for this study. Participants in the initial visit category were those attending the genetic counseling clinical appointment due to a family history of pancreatic cancer and were counseled about having endoscopic ultrasound surveillance for the first time. They were scheduled or had their initial EUS when first enrolled into this study. Individuals in the return visit group were those who were identified as high-risk due to a family history of pancreatic cancer and who had

already had at least one endoscopic ultrasound. These individuals were counseled previously and were having follow-up EUS at the time they were enrolled in this study. Participants in the comparison group were those who had been identified as having any signs or symptoms relating to the pancreas, which prompted their physician to order a diagnostic EUS. Once enrolled, all patients were given a de-identified code to track their questionnaires. All IDs started with PA to signify that they were part of the PAGER study and then a number that was specific to them.

4.2 INSTRUMENT

4.2.1 Validation

The content, format, and validity of the questionnaires were developed based on the Champion Health Belief Model (CHBM) scales. Questions were constructed using input from the CHBM scales for breast and cervical cancer (Guvenc et al., 2010). Changes in wording were made to make items applicable to pancreatic cancer and surveillance, but the overall theme of each question was kept intact.

4.2.2 Questionnaires

We developed the "Feelings about Cancer Risk and Endoscopic Ultrasound" Questionnaire based on a review of current literature. The survey instrument consisted of 16 questions, divided into five sub-categories: level of worry, risk perception, family history, social support, and health intervention. The questionnaire had four questions addressing the individuals' level of worry,

six questions addressing their risk perception, two questions concerning their family history, two questions about the individuals' social support, and two questions addressing the health intervention. Individuals were asked to assess their feelings about each question using a Likert scale. The scale gave individuals the chance to strongly disagree (1), disagree (2), neutral (3), agree (4), and strongly agree (5) with each statement. Questions addressing family history did not pertain to the comparison cohort, so a N/A (0) option was also available. High-risk individuals (cases) were asked an additional five questions, used to assess their referral route, motivation for seeking genetic counseling and EUS, whether or not they decided to pursue an EUS, and whether or not their feelings about their cancer risk or their level of worry changed since their first EUS. Each questionnaire also had a section where participants could write any additional comments for the researchers. Questionnaires can be seen in Appendix B.

All participants, regardless if they were a case or comparison, were given two questionnaires as part of their enrollment. Both questionnaires used the same questions to allow for analysis. For case participants, the first questionnaire was given either at the conclusion of the genetic counseling appointment while the patient was in the office or during their pre-op time in the GI Lab. Participants were asked to complete the questionnaire before leaving the counseling session or being taken in for their procedure. Before the case participant was taken for EUS, the second questionnaire was placed with their personal belongings or with a family member or friend, along with a self-addressed stamped return envelope. Participants were asked to complete the second questionnaire after the procedure and return it upon completion.

4.3 DATA COLLECTION

Data were collected between September 2011 and March 2012. Questionnaires took approximately five to ten minutes to complete. Data input occurred as the second questionnaires were received. Fifteen of the 20 (75%) participants returned the second questionnaire. Those who did not immediately return the second questionnaire were contacted after a period of time. At that point, if the individuals were still interested in participating, then the questionnaire was either emailed to them for completion, or the questions were read aloud to them over the phone. Along with the information gathered through their answers, information was also gathered about the participant's demographics. Information including the participants' age, gender, ethnic background, and EUS findings were collected. For the high-risk individuals, family history and genetic status were also collected.

4.4 DATA ANALYSIS

The results of this study were analyzed using three different methods. The majority of the data was collected using the answers from the Likert scale portion of the questionnaire. Descriptive statistics was used for this data. It is a method typically used for smaller studies as a way to quickly display and interpret the data (Rosner, 2011). Using this method, researchers can conclude what trends may warrant a more detailed look in future research studies. Data was inputted into an Excel spreadsheet and the mean value was calculated for each question. Charts were created to keep the data as self-contained as possible, which is the preferred method when using descriptive statistics (Rosner, 2011). For this study, the arithmetic mean was used to

evaluate the trends for each question. It was determined that the mean was the most logical way to analyze the data because the data was less likely to be affected by extreme values, which is a limitation of the arithmetic mean. Trends were recorded from the arithmetic mean and noted for any score change.

To evaluate for statistical significance, the two cohorts were combined to give a larger sample size. A one-tailed t-test was performed on the combined data to assess the significance before and after the procedure (Rosner, 2011). For this study, a critical value of 0.05 was used to test for significance.

The narrative responses were analyzed by thematic analysis. This method is used for open-ended responses by participants when a clear answer is not apparent, as in a numeric response (Braun and Clark, 2006). It is usually chosen as an analytic method because it is more flexible and relatively easy for a researcher to learn. However, limitations of thematic analysis are that the methodology is not well defined and thus open to interpretation. For the responses received, thematic analysis is the method most applicable. Within the narrative responses, themes were noted and compared with the overall trends from the descriptive statistical analysis to see if any similarities were seen. This study may act as a pilot for a future, larger study, in the hopes of including more families at high risk so that the results may reach statistical significance.

5.0 RESULTS

5.1 SAMPLE DESCRIPTION

A total of 33 individuals (20 cases and 13 comparisons) provided informed consent for this study. With a combination of returned questionnaires and follow-up phone calls, 26 participants completed both questionnaires (15 cases and 11 comparisons) for an overall complete participation rate of 87%. Demographic, family medical history, and pertinent personal medical information were recorded for these individuals.

The average age of the case individuals was 58.4 years, with a range of 35 – 74 years. Seventy-three percent of the cases were female, and all individuals reported race as Caucasian. Genetic status and family history of these cases were also recorded. Complete pedigrees of these 15 cases can be found in Appendix D. Two carried mutations in *CKDN2A* (*p16*) and had an extensive family history of pancreatic cancer. Two carried mutations in *BRCA1*, both of whom had first-degree relatives with pancreatic cancer. One case individual carried a maternally transmitted *BRCA2* mutation, though her father had pancreatic cancer. Two case individuals were diagnosed with Lynch syndrome; one carried an *MSH6* mutation and the other carried an *MSH2* mutation. There were two cases with strong family history but no known gene mutation. In these families, one case was tested and not found to carry a *BRCA* mutation; in the other

family, a sister of the proband tested negative for *BRCA* mutation. All other cases were diagnosed with FPC. There were no cases in this study that came from the same kindred.

EUS findings were also recorded. A short description of the EUS findings can be found in the table below.

Table 1. EUS findings from case cohort

STUDY NUMBER	GENETIC STATUS	EUS FINDINGS
PA1652	*BRCA2*+	12mm cystic lesion, IPMN
PA1324	FPC	Subtle nodular change
PA0469	FPC	Multi-focal cysts, not malignant
PA0998	FPC	4x3mm cystic lesion, not malignant
PA1091	*BRCA*- sister	24mm benign lipoma
PA0557	*MSH6*+	Multiple cystic lesions
PA0486	*BRCA*-	Premalignant IPMN
PA0527	*p16*+	2 small cystic lesions
PA1559	*p16*+	5mm lesion
PA1680	FPC	Normal pancreas
PA0296	FPC	2x1mm cystic mass
PA1087	*MSH2*+	Normal pancreas
PA0892	*BRCA1*+	Normal pancreas
PA1027	*BRCA1*+	Normal pancreas
PA1729	*BRCA* testing not covered	Pancreas cyst vs. pseudocyst

The average age of the comparison group was 67.4 years, with a range of 53 – 90 years. Sixty-four percent of the comparisons were female and all individuals were Caucasian. The EUS findings were also recorded to assess medical indication and outcome. A short description of those findings can be found in the table below.

Table 2. EUS findings from comparison cohort

STUDY NUMBER	EUS FINDINGS
PA1597	36x25mm cyst, not malignant
PA1679	5x4mm cystic lesion
PA1596	Large cyst, not malignant
PA1705	Mild dilation of main pancreatic duct
PA1743	Negative for chronic pancreatitis
PA1763	25mm IPMN
PA1828	Serous cystadenoma
PA1880	Pancreatic mass
PA1883	Pancreatic mass
PA1852	Small neuroendocrine tumors
PA1750	Large cystic lesion, no solid component

5.2 SUPPLEMENTAL QUESTIONNAIRE

High-risk individuals were also given a supplemental questionnaire that contained five questionnaires to assess specific topics in that population. Of the 15 high-risk individuals in this study, five participants were being evaluated for the first time, and ten were returning for follow-up surveillance. All 15 individuals were asked how they found out about genetic counseling for high-risk families. Six indicated they were referred through their doctor. Three individuals said a family member informed them. Three indicated another route not given as a choice. Participants were permitted to choose more than one option. One heard of counseling from his family and physician, one indicated both the Internet and doctor, and the last heard of genetic counseling through the Internet and a second unidentified option. All individuals were also asked what their top motivation was for seeking genetic counseling for pancreatic cancer. Ten individuals indicated they were looking for information related to their personal risk for pancreatic cancer. One participant was looking for risk information related to her family. One individual was concerned that he had pancreatic cancer and was looking for a diagnosis. Two

individuals indicated they wanted information about their personal risk as well as information for the entire family. One individual was using the session for familial information and as a means of having the EUS.

Initial participants who were being seen at the genetics clinic were also asked if they would be having the EUS after hearing the information in the session. All five individuals elected to schedule their EUS procedure after the genetic counseling session. Thus, the second question was not applicable.

The ten returning individuals were asked to recall how the EUS affected their level of worry and cancer risk perception since they had their first EUS. Three participants indicated that their level of worry and cancer risk perception had decreased since they started surveillance. One participant indicated his worry level and risk perception had both increased since starting EUS. Five individuals indicated both aspects had remained the same since starting the protocol. And one individual indicated that while her cancer risk perception had remained the same, her level of worry increased.

Table 3. Supplemental questionnaire answers

QUESTION	INITIAL VISITS (# of participants)	RETURN VISITS (# of participants)
How did you find out about genetic counseling for individuals with a family of pancreatic cancer?	Family = 2 Doctor = 3	Family = 1 Doctor = 3 Other = 3 Family and Doctor = 1 Doctor and Internet = 1 Internet and Other = 1
What was your top motivation for coming to the Pancreas Clinic?	Personal cancer risk = 4 Cancer risk for family = 1	Personal cancer risk = 6 Find out if I have cancer = 1 Personal and Family risk = 2 Family and to have EUS = 1
Are you going to have the endoscopic ultrasound?	Yes = 5	
How has your you feeling about your cancer risk and worry changed from the first time you had an EUS?		Both decreased = 3 Both stayed the same = 5 Both increased = 1 Risk perception increased, worry stayed the same = 1

5.3 ANALYSIS OF CASES VERSUS COMPARISONS

The first section of analysis focuses on the trends of the two participant groups. The trends were scored for each question before and after the endoscopic ultrasound.

5.3.1 Level of worry

Table 4 shows the data on level of worry for both cases and comparisons. An average was calculated for both groups.

Table 4. Cases versus comparisons level of worry

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
I feel I will get pancreatic cancer some time during my life.	2.93	1.72	2.93	1.95
The thought of pancreatic cancer scares me.	3.73	4.55	4.13	4.27
I worry more about my risk since watching family members fight pancreatic cancer.	4.20	0.64	4.00	0.55
I am afraid of the endoscopic ultrasound, for fear of a bad result.	1.73	2.45	1.60	2.00

LEGEND	N/A	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
	0	1	2	3	4	5

Both groups showed a decreased trend in their fear of the procedure itself. The cases group had a decrease of 0.13, while the comparison group had a decrease of 0.45.

In contrast, the groups showed opposing trends when asked about their fear of a pancreatic cancer diagnosis. The case group increased by 0.40 after the procedure, while the

comparison group decreased 0.28. The comparison group also scored higher, overall, than the case group.

5.3.2 Risk perception

Table 5 shows the data on the cancer risk perception for both populations. Averages were calculated for both groups.

Table 5. Cases versus comparisons risk perception

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
If I develop pancreatic cancer, I will not live longer than 1 year.	2.80	3.27	2.73	2.91
I understand the benefits and limitations of the endoscopic ultrasound.	4.27	3.36	4.33	3.27
I have control over my pancreatic cancer risk by having the endoscopic ultrasound.	2.87	2.91	3.40	3.73
Having the endoscopic ultrasound can find pancreatic cancer early.	4.27	3.91	4.33	3.64
If my pancreatic cancer is found early because of the endoscopic ultrasound, I will live longer.	4.07	3.09	3.83	3.77
Having the endoscopic ultrasound gives me the feeling of a lower risk for pancreatic cancer.	3.20	3.18	3.47	3.82

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Three of the questions related to the individuals' view on their cancer risk had a notable trend. The question related to the control a person has over their cancer risk. Both groups seemed to feel they had more control over their risk after the EUS. The case group's mean increased by 0.53 while the comparisons' mean increased by 0.82. Both groups also shared a similar trend

regarding the perception that the EUS gives them a feeling of a lower cancer risk. The cases' score increased by 0.27, while the comparisons' score increased 0.64.

For the question pertaining to life span as it relates to early diagnosis by EUS, the case group trended slightly lower after the EUS, with a decrease of 0.24. However, the comparisons had a trend that moved in the opposite direction. The comparisons' mean increased after the EUS by 0.68.

5.3.3 Family history

Table 6 shows the data on the impact of family history for both cases and comparisons. An average was calculated for both groups.

Table 6. Cases versus comparisons family history

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
Having family members with pancreatic cancer increases my chance to develop it.	4.47	1.18	4.33	1.55
I want to encourage family members to have the endoscopic ultrasound.	4.20	3.81	4.33	2.45

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

As expected, family history seemed to hold one of the biggest trend differences between the two groups. The comparison cohort had a decrease of 1.36 when asked if they will encourage other family members to pursue EUS. This is compared to a steady trend for the case cohort before and after the procedure.

5.3.4 Social Support

Table 7 shows the data on social support for both populations. Averages were calculated for both groups.

Table 7. Cases versus comparisons social support

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
My family encouraged me to have pancreatic cancer surveillance.	3.27	1.36	3.40	1.09
If I get pancreatic cancer, I do not want to be a burden on my family	4.00	4.27	4.13	4.18

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Social support is an important aspect to pancreatic cancer, because of the seriousness of the disease and the impact it can have on an entire family. As expected, the encouragement of family members showed a trend difference between the two groups. While the score change before and after the procedure was not notable, the overall score difference shows the trend difference between the two populations. The cases trended almost two points higher than the comparisons in both questionnaires.

As expected, both groups responded to the impact the disease has on the family once a diagnosis has been made. This relates to the perceived seriousness of pancreatic cancer and is noted in the high trend numbers from both groups for both questionnaires.

5.3.5 Health Intervention

Table 8 shows the data on health intervention for both cases and comparisons. An average was calculated for both groups.

Table 8. Cases versus comparisons health intervention

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
I want to do everything I can to prevent pancreatic cancer.	4.73	4.91	4.67	4.82
If developing pancreatic cancer is in my future, then having the endoscopic ultrasound will not change that.	2.27	2.91	3.07	2.64

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Both groups responded highly to the use of EUS for medical intervention purposes. We would not expect this data to be any lower as these individuals are those that are pursuing EUS. There was an opposite trend noted in the final question in this group. The question acknowledges the idea of a potential barrier in the high-risk population. The cases trended higher after the EUS (0.80), while the comparisons had a decrease in trend (0.27) after the procedure.

5.4 ANALYSIS OF FAMILIAL CASES BY MUTATION STATUS

The following portion is an evaluation of the trends before and after the endoscopic ultrasound of only the familial patients. The familial patients were divided into two groups, those with an identified germline mutation and those without a germline mutation. In this section, the

abbreviation “with” in the tables signifies those familial patients with an identified germline mutation and “without” signifies the familial patients without an identified germline mutation.

5.4.1 Level of worry

Table 9 shows the data on level of worry for both familial cases with and without a germline mutation. An average was calculated for both groups.

Table 9. Familial level of worry

	BEFORE EUS		AFTER EUS	
	WITH	WITHOUT	WITH	WITHOUT
I feel I will get pancreatic cancer some time during my life.	2.71	3.12	3.45	3.00
The thought of pancreatic cancer scares me.	3.29	4.13	3.86	4.38
I worry more about my risk since watching family members fight pancreatic cancer.	4.00	4.38	3.86	4.13
I am afraid of the endoscopic ultrasound, for fear of a bad result.	1.86	1.63	1.71	1.50

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Increased trends were seen with both populations when asked about their fear of pancreatic cancer after the endoscopic ultrasound. Those with a germline mutations increased by 0.57, while those without a germline mutation increased by 0.25. It is also important to note the overall score difference between the two groups. Although those without a mutation increased by a smaller amount, their overall score was higher than those with a mutation.

Opposing trends were noted when asked about their worry about developing pancreatic cancer at some point in their lifetime. Those with a germline mutation increased by 0.74, while those without an identified mutation decreased by 0.12.

5.4.2 Risk perception

Table 10 shows the data on the cancer risk perception for both populations. Averages were calculated for both groups.

Table 10. Familial risk perception

	BEFORE EUS		AFTER EUS	
	WITH	WITHOUT	WITH	WITHOUT
If I develop pancreatic cancer, I will not live longer than 1 year.	2.29	3.25	2.43	3.00
I understand the benefits and limitations of the endoscopic ultrasound.	4.43	4.13	4.43	4.25
I have control over my pancreatic cancer risk by having the endoscopic ultrasound.	3.29	2.50	3.86	3.00
Having the endoscopic ultrasound can find pancreatic cancer early.	4.43	4.13	4.29	4.38
If my pancreatic cancer is found early because of the endoscopic ultrasound, I will live longer.	3.86	4.25	3.79	3.88
Having the endoscopic ultrasound gives me the feeling of a lower risk for pancreatic cancer.	3.00	3.38	3.29	3.63

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Both populations felt they had more control over their cancer risk by having EUS. Those individuals with a mutation increased by 0.57 and those without increased by 0.50. Both populations also felt the procedure gave them the feeling of a lower cancer risk. Mutation carriers increased by 0.38 after the procedure and those without an identified mutation increased by 0.25. Both groups were also asked if they would live longer if pancreatic cancer were found by EUS. Those individuals with a mutation decreased by 0.07, and those without a mutation decreased by 0.37.

5.4.3 Family history

Table 11 shows the data on the impact of family history for both familial cases with and without a germline mutation. An average was calculated for both groups.

Table 11. Familial family history

	BEFORE EUS		AFTER EUS	
	WITH	WITHOUT	WITH	WITHOUT
Having family members with pancreatic cancer increases my chance to develop it.	4.43	4.50	4.43	4.25
I want to encourage family members to have the endoscopic ultrasound.	4.38	4.13	4.43	4.25

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Both populations were asked about the impact of a family history of pancreatic cancer on their individual pancreatic cancer risk. Those individuals with a germline had stable score, while those without a germline mutation decreased by 0.25.

5.4.4 Social Support

Table 12 shows the data on social support for both populations. Averages were calculated for both groups.

Table 12. Familial social support

	BEFORE EUS		AFTER EUS	
	WITH	WITHOUT	WITH	WITHOUT
My family encouraged me to have pancreatic cancer surveillance.	3.00	3.50	3.57	3.25
If I get pancreatic cancer, I do not want to be a burden on my family	3.86	4.13	3.86	4.38

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Opposing trends were noted when asked whether or not their family encouraged them to have EUS. Those with a germline mutation increased by 0.57 after the procedure, while those without a mutation decreased by 0.25.

5.4.5 Health Intervention

Table 13 shows the data on health intervention for both familial cases with and without a germline mutation. An average was calculated for both groups.

Table 13. Familial health intervention

	BEFORE EUS		AFTER EUS	
	CASES	COMPARISONS	CASES	COMPARSIONS
I want to do everything I can to prevent pancreatic cancer.	4.71	4.75	4.71	4.63
If developing pancreatic cancer is in my future, then having the endoscopic ultrasound will not change that.	2.43	2.13	2.86	3.25

LEGEND	N/A 0	Strongly Disagree 1	Disagree 2	Neutral 3	Agree 4	Strongly Agree 5

Similar trends were noted when asked about an inevitable pancreatic cancer diagnosis, even with EUS. The familial group with an identified mutation increased by 0.43. The familial group without a mutation increased by 1.12.

5.5 ANALYSIS OF COMBINED CASES AND COMPARISONS

For the purposes of statistical analysis, the case and comparison groups were combined to evaluate whether there was any statistical significance pre- and post-procedure. Table 14 includes the p-values from the questions before and after the procedure.

Table 14. T-test analysis of combined groups

STATEMENT	P-value
I feel I will get pancreatic cancer some time during my life.	0.486
The thought of pancreatic cancer scares me.	0.649
If I develop pancreatic cancer, I will not live longer than 1 year.	0.457
Having family members with pancreatic cancer increases my chance to develop it.	0.603
I want to do everything I can to prevent pancreatic cancer.	0.490
I worry more about my risk since watching family members fight pancreatic cancer.	0.256
My family encouraged me to have pancreatic cancer surveillance.	0.901
I understand the benefits and limitations of the endoscopic ultrasound.	1.000
I am afraid of the endoscopic ultrasound, for fear of a bad result.	0.258
If developing pancreatic cancer is in my future, then having the endoscopic ultrasound will not change that.	0.187
I have control over my pancreatic cancer risk by having the endoscopic ultrasound.	0.047
Having the endoscopic ultrasound can find pancreatic cancer early.	0.664
If my pancreatic cancer is found early because of the endoscopic ultrasound, I will live longer	0.594
I want to encourage family members to have the endoscopic ultrasound.	0.471
If I get pancreatic cancer, I do not want to be a burden on my family.	0.857
Having the endoscopic ultrasound gives me the feelings of a lower risk for pancreatic cancer.	0.1334

Using this statistical method, one question showed statistical significance before and after the procedure. The question with significance less than 0.05 was the question related to the feeling of control over the pancreatic cancer risk by having the endoscopic ultrasound.

5.6 NARRATIVE RESPONSES

Both questionnaires gave participants the opportunity to add additional comments in areas they felt were not covered. All comments received were recorded from high-risk patients. A total of eight comments were recorded, including three participants who added comments to both questionnaires. A complete transcription of comments can be viewed in Appendix C.

All responses were categorized into one of the four Health Belief Model categories. PA0486's comments seemed to address issues related to perceived susceptibility. She mentions that her chances of getting pancreatic cancer are out of her control and she understands her inherent susceptibility. She understands the constant surveillance of her cysts and has had breast cancer in the past. PA1091 touched on the idea of perceived seriousness. He has a strong family history of pancreatic cancer and was relatively scared of the diagnosis. He indicated that pancreatic cancer is a silent killer. He was comparing warning signs of pancreatic cancer with other more common cancers, with more identifiable symptoms. Four individuals (PA0527, PA1729, PA0469, PA0998) gave comments that seemed related to perceived benefits. All individuals felt that early detection of pancreatic cancer was an important aspect of surveillance. Some believed in the EUS and it has become part of their lives, since some have had multiple surveillance procedures due to a hereditary susceptibility to cancer. One individual discussed that while he sees the benefit in surveillance, he cannot get the rest of his family to even discuss it. He has tried different strategies and cannot "get through to them". The last category, perceived barriers, encompassed responses from two individuals (PA0215 and PA0557). Both individuals noted that they had pancreatic changes that were not seen on EUS, but on MRI/CT.

6.0 DISCUSSION

Through the use of the Health Belief Model, this study has examined individuals' motivation for attending a high-risk clinic as well as evaluating the pancreatic cancer risk perception and level of worry in a high-risk, healthy population. This is one of the few studies that have looked at the psychosocial impacts of the endoscopic ultrasound in this small population.

The first goal of this study was to identify familial individuals' top motivation for attending the high-risk pancreas clinic. Most high-risk individuals found out about the clinic through either their family or doctor. This is consistent with how individuals are referred to the clinic. The top motivation for attending the clinic in ten of 15 participants was to find out more information about their personal cancer risk. This is consistent with other studies (Axilbund et al., 2005) that showed individuals want information about their cancer risks. Although this same study has shown that individuals were frustrated with the lack of definitive information and genetic testing available for some pancreatic cancer kindreds.

The second goal of this study was to assess the cancer risk perception and level of worry before and after endoscopic ultrasound. Participants were asked questions that evaluated different aspects of their worry level. Both the comparison and case cohorts shared a similar trend decrease in regards to their fear of the procedure. Previous studies have shown this same trend, with a decrease in the level of worry, particularly in the unaffected population (Price et al., 2007). It seems reasonable that the case cohort would be fearful of the procedure due to the

impact of their family history. It seems the comparison group may have viewed some barriers of the procedure. This is likely due to the fear of a cancer diagnosis as a result. Going in with a suspected pancreatic abnormality for potential diagnosis could have elicited fear about the procedure itself.

Opposing trends were noted in the cohorts when asked about their fear of a pancreatic cancer diagnosis. This was also noted when the familial groups were separated by mutation status. Those without a mutation had a higher overall score than those with a germline mutation. The case cohort may still worry about their risk because of their family history. They have an idea of how serious the condition is and are fearful of developing it. Studies have shown that the strongest predictor of cancer worry was a patient's overall increased anxiety (Price et al., 2007). However, this finding seems to be in contrast with other studies evaluating cancer worry. Research has shown an overall decrease of cancer worry after genetic counseling and surveillance (Keller et al., 2008). The comparison group followed the trend expected from previous research which may be because the diagnostic EUS was negative for pancreatic cancer.

Overall, the case and comparison cohorts showed similar trends related to the EUS and their cancer risk perception. Participants reported feeling greater control over their pancreatic cancer risk by having the EUS. This was also noted in the familial trend comparisons. Additionally, this was the only question that showed statistical significance when both cohorts were combined. This is an important aspect for both populations. It is possible that an individual with a strong family history of a disease or an individual with a pancreatic abnormality may feel that they do not have control over their health and are just being told where to go for medical advice. The fact that this procedure seems to have a positive impact on these individuals means they might be acknowledging the benefits, even if the medical professionals

are still unsure about its validity in certain cases. This trend is similar to a theme noted in Keogh et al. A group of women at high-risk for breast cancer, for an unknown reason, explained that they were concerned about their breast cancer risk and were as vigilant as possible. Their thought process was driven by their concern for their cancer risk and their belief that their actions may reduce their risk.

Participants were also asked a more direct question about their pancreatic cancer risk to evaluate their perceived risk. Participants expressed that this procedure gave them a feeling of a lower cancer risk. They accepted the findings from the EUS as fact: they did not have cancer. These similar trend were also noted when the familial groups were divided. This is consistent with previous studies that have noted a lower risk perception after genetic counseling, which included a discussion on surveillance (Bjorvatn et al., 2007).

In regards to the participants' understanding of the benefits and limitations of the EUS, the case and comparison cohorts differed in their trends. One possible reason for this difference is because of the significantly different conversation with each cohort of patients about the procedure itself. The limitations of the EUS are quite different when looking at a potentially healthy pancreas as opposed to looking for a suspected pancreatic change. In the high-risk healthy cohort, the limitations are explained in greater detail because the effectiveness of EUS for this service is not well understood. It is unclear whether or not surveillance will improve survival, which is something that is not explained to the comparison cohort, since the test is being used for diagnostic purposes (Canto et al., 2012; Poley et al., 2009). For the comparison cohort, the limitations are not as extensive because the physician knows what to look for in the pancreas. In addition, the limitations may not be as much of a concern for the comparison cohort because they could be facing a cancer diagnosis. The intricacies of the procedure may not be as

much of a concern. The benefits and positive feelings outweigh the barriers and potential limitations of the procedure. This result is in contrast with previous studies that have found that patients could not recall surveillance information and whether or not they had the option of surveillance (Bjorvatn et al., 2007). This study claims that surveillance may not have been a main part of the counseling session. However, the conversations with the patients in this study center around surveillance and prevention, since many times genetic testing cannot be offered to confirm their true risk.

Participants were also asked about early detection of pancreatic cancer and its relation to life span, and the case and comparison cohorts trended in opposite directions. This difference in trend may be attributed to the impact of the family history of the high-risk patients. When the familial cohort was separated by germline mutations, both groups showed a decrease trend for this question, showing there is no difference based on mutation status. These individuals already have a pre-conceived idea of their susceptibility to pancreatic cancer, and no matter how beneficial the EUS may be, these individuals may still allow their personal experiences to drive their risk perception. This is common trend noted throughout this study and in past research, where patients cannot separate their qualitative cancer risk and their emotionally driven cancer risk (Keogh et al., 2011).

Questions relating to the impact of family history and familial support seemed to show the most disparity in the trends between the two groups. The effects of family history on the participant's risk to develop pancreatic cancer showed trend differences between the case and comparison cohorts. Previous studies (Axilbund et al., 2005) have shown that patients from pancreatic cancer kindreds find genetic counseling valuable. The results of the current study seem to suggest that family history is a strong component for a patient's risk perception, even if

it is opposite of what is stated by a medical professional. This result was seen in previous studies as well, where women from unexplained, high-risk breast cancer families could not separate their perceived risk from their emotional response to their risk (Keogh et al., 2011). When evaluating surveillance, high-risk kindreds would be more likely to band together and seek out surveillance for a disease affecting their relatives. An individual with no family history would likely not receive surveillance and would only have the influence of the family as it relates to having the EUS for diagnostic purposes. The support of an individual's family also showed a trend for the case cohort as it relates to the potential seriousness of pancreatic cancer. Many of these individuals were encouraged by their family to have the procedure. Perhaps if they did not have the support of their family, they would not have sought surveillance.

Certain aspects of the health intervention portion showed trend differences between the two groups. The case cohort seemed to be driven by the emotional impact of pancreatic cancer, regardless of having the EUS. This emotional impact is quite evident; this population also scored high when asked if they wanted to do everything they could to prevent pancreatic cancer. It seems that, although this cohort wants to pursue all surveillance available, their perception of their future health is more influenced by their family history. They likely have family members who had undergone surveillance and still battled pancreatic cancer. They may also have a family history of pancreatic cancer that still remains despite the result of a single EUS procedure being normal. Keogh et al. described this as the fatalism group. This group viewed their risk as inevitable, and was not diligent with surveillance, which is different than this population. While they may have the fatalistic view because of their familial history, they continued to pursue EUS.

6.1 LIMITATIONS

The results presented in this study are preliminary and several limitations are present. Firstly, the sample size is small and does not lend itself to results with statistical significance. The pancreatic cancer patient population is also small, with the hereditary predisposition syndrome population being even smaller. It may take a much longer recruitment period to capture a greater number of high-risk individuals.

Secondly, all participants in this study were Caucasian. There is a question about whether the trends seen in this study would translate to other ethnic, racial, or socioeconomic groups.

Thirdly, these individuals were also those who were actively seeking surveillance and genetic counseling. This was an unavoidable limitation because recruitment was done through the PAGER study that required participants to be in a UPMC facility. This study did not capture those individuals who may be at high-risk but who are not actively seeking medical interventions.

Lastly, insurance coverage for a surveillance procedure in the healthy population where an established protocol has not been established has been a problem. Some cost-effectiveness vs. benefit studies have been done (Stoita et al., 2011) but more information needs to be collected. With an extended recruitment period, there may be individuals who cannot fully participate in the study because their insurance will not cover the procedure.

6.2 FUTURE STUDIES

As previously stated, this study is intended to be the stepping stone towards a larger study in the hopes that a extended recruitment period could enroll more individuals from both patient populations. A power calculation can be done to determine the number of participants needed to achieve statistical significance. An important feature of this study is those high-risk individuals who do not pursue genetic counseling and/or surveillance. Since one individual expressed his frustrations with his family for not pursuing EUS, future studies may focus on the proband's family members who are not seeking surveillance. If we can identify those people, we may be able to compare potential barriers within a family.

We also would have liked to assess their personal risk perception on a scale from one to ten. If the patients can quantify their risk, this may give researchers a better understanding of the trends being seen in the data. It is also important to understand their risk perception when there are no survivors in the family. We may be able to evaluate the perceived risk of familial pancreatic cancer individuals to other individuals from a hereditary cancer family that tends to have more survivors, like HBOC or HNPCC.

Future studies will also help healthcare providers give more accurate counseling to this population. The hope is that we can better understand the procedure itself as well as the impact it has on this population.

7.0 CONCLUSIONS

This study is the first of its kind, and is the stepping-stone in understanding the psychosocial impact of surveillance for this disease in this specific population. Many studies (Keller et al., 2005; Meiser et al., 2008) have been done looking at the capability and psychosocial impact of more regularly used surveillance methods, like mammography and colonoscopy. The hope is that the EUS can be included in the list with those procedures as more research is performed and more information is gathered.

APPENDIX A

INSTITUTIONAL REVIEW BOARD LETTER OF APPROVAL

University of Pittsburgh

Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508
(fax) http://www.irb.pitt.edu

Memorandum

To: Randall Brand, MD
From: Margaret Hsieh, MD, Vice Chair
Date: 10/5/2011

IRB#: MOD07030072-28 / PRO07030072
Subject: The Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study - A prospective cohort study of patients at risk or having pancreatic disease

The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 9/27/2011
Expiration Date: 4/20/2012

For studies being conducted in UPMC facilities, no clinical activities that are impacted by the modifications can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B

QUESTIONNAIRES

B.1 LIKERT QUESTIONNAIRE

The attached questionnaire is the set of questions all participants answered. Participants answered this questionnaire after genetic counseling/before the EUS and after the EUS.

Feelings about Cancer Risk and Endoscopic Ultrasound

You told us that you plan to have the endoscopic ultrasound, please circle one (1) number that best describes your feeling about each statement.

Statement	N/A	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I feel I will get pancreatic cancer some time during my life.	0	1	2	3	4	5
The thought of pancreatic cancer scares me.	0	1	2	3	4	5
If I develop pancreatic cancer, I will not live longer than 1 year.	0	1	2	3	4	5
Having family members with pancreatic cancer increases my chance to develop it.	0	1	2	3	4	5
I want to do everything I can to prevent pancreatic cancer.	0	1	2	3	4	5
I worry more about my risk since watching family members fight pancreatic cancer.	0	1	2	3	4	5
My family encouraged me to have pancreatic cancer surveillance.	0	1	2	3	4	5
I understand the benefits and limitations of the endoscopic ultrasound.	0	1	2	3	4	5
I am afraid of the endoscopic ultrasound, for fear of a bad result.	0	1	2	3	4	5
If developing pancreatic cancer is in my future, then having the endoscopic ultrasound will not change that.	0	1	2	3	4	5
I have control over my pancreatic cancer risk by having the endoscopic ultrasound.	0	1	2	3	4	5
Having the endoscopic ultrasound can find pancreatic cancer early.	0	1	2	3	4	5
If my pancreatic cancer is found early because of the endoscopic ultrasound, I will live longer	0	1	2	3	4	5
I want to encourage family members to have the endoscopic ultrasound.	0	1	2	3	4	5
If I get pancreatic cancer, I do not want to be a burden on my family.	0	1	2	3	4	5
Having the endoscopic ultrasound gives me the feelings of a lower risk for pancreatic cancer.	0	1	2	3	4	5

B.2 INITIAL VISIT ADDITIONAL QUESTIONNAIRE

Feelings about Cancer Risk and Endoscopic Ultrasound: Initial Visit

We are trying to better understand feelings about pancreatic cancer risk when a person has a higher risk because of their family's medical history. This short questionnaire should take about 5 minutes. Please check the answer(s) that best describe your feelings about the question at hand. Thank you very much for your participation in our important research.

1. **How did you find out about genetic counseling for individuals with a family history of pancreatic cancer? Please check all that apply.**

   ☐ Family
   ☐ Doctor
   ☐ Internet
   ☐ Friend
   ☐ Other (please specify) _____

2. **What was your TOP motivation for coming to the Pancreatic Clinic? Please check one.**

   ☐ I wanted to learn information about my personal pancreatic cancer risk.
   ☐ I wanted to learn information about pancreatic cancer risk for my family members.
   ☐ I wanted to have the endoscopic ultrasound.
   ☐ I wanted to find out if I have pancreatic cancer.
   ☐ Other (please specify) _____

3. **Are you going to have the endoscopic ultrasound? Please check one.**

   ☐ Yes, it is scheduled for _____ (Skip to the next section)
   ☐ Yes, I plan to schedule. (Skip to the next section)
   ☐ Not sure.
   ☐ No.

4. **What is the reason that you are not having the endoscopic ultrasound? Please check one. (Once answered, you may stop here and take your questionnaire to the front desk)**

   ☐ My risk for pancreatic cancer is not considered high enough.
   ☐ My insurance will not cover the procedure.
   ☐ I feel scared of having the procedure.
   ☐ I am worried about what the doctor will find.
   ☐ I do not think it is worthwhile or will make a difference.
   ☐ Other (please specific) _____

B.3 RETURN VISIT ADDITIONAL QUESTIONNAIRE

Feelings about Cancer Risk and Endoscopic Ultrasound: Return Visit

We are trying to better understand feelings about pancreatic cancer risk when a person has a higher risk because of their family's medical history. This short questionnaire should take about 5 minutes. Please check the answer(s) that best describe your feelings about the question at hand. Thank you very much for your participation in our important research.

1. **How did you find out about genetic counseling for individuals with a family history of pancreatic cancer? Please check all that apply.**

   ☐ Family
   ☐ Doctor
   ☐ Internet
   ☐ Friend
   ☐ Other (please specify) _____

2. **What was your TOP motivation for coming to the Pancreatic Clinic? Please check one.**

   ☐ I wanted to learn information about my personal pancreatic cancer risk.
   ☐ I wanted to learn information about pancreatic cancer risk for my family members.
   ☐ I wanted to have the endoscopic ultrasound.
   ☐ I wanted to find out if I have pancreatic cancer.
   ☐ Other (please specify) _____

3. **How has your feeling about your cancer risk and worry changed from the first time you had a EUS? Check all that apply.**

   Since my first EUS…
   ☐ My feeling about my risk to have pancreatic cancer has increased.
   ☐ My feeling about my risk to have pancreatic cancer has decreased.
   ☐ My feeling about my risk to have pancreatic cancer has remained the same.

   Since my first EUS…
   ☐ I worry more about being diagnosed with pancreatic cancer.
   ☐ I worry less about being diagnosed with pancreatic cancer.
   ☐ I worry about the same about being diagnosed with pancreatic cancer.

APPENDIX C

NARRATIVE TRANSCRIPTIONS

C.1 PRE-TEST RESPONSES

PA1091: “All other cancers give you a warning. You might bleed or hurt. But not pancreatic cancer.”

PA0527: “I strongly believe this procedure can find cancer early and I can live longer because of it.”

PA1729: “Having a background [and] professional experience with EUS helps my understanding. I feel that the possible early pancreatic cancer detection “or risk detection” increases/improves my chances of long term survival.”

PA0215: “I am on a 3 mo. schedule [for] EUS-MRI. If I understand correctly, the cysts were not seen on the EUS. It showed on the MRI.”

C.2 POST-TEST RESPONSES

PA0557: “As a member of the mental health profession (an LCSW and an RN), I am pleased that you are considering the impact that emotional health has on the development of disease. The EUS is one of many screening tests I have since I have a history of personal cancer along with numerous first-degree family members with cancer, including pancreatic (brother). I also have Lynch syndrome. Of my many screenings including CAT, MRI, ultrasounds, etc, the EUS has become one of the most important to me for monitoring my diffuse pancreatic cysts. Even though I realize the importance of constant surveillance in this disease, so many continual screenings can put much more stress on a patient and create anxiety while awaiting results. However, after several years, this has just become part of my life!”

C.3 PRE- AND POST-TEST RESPONSES

PA0998: “I am glad that early detection work is being done. It may help my two nieces who are at very high risk, and many others.”

“Full speed ahead – you are on the right track.”

PA0486: “Cysts to me aren’t as scary because I have had breast cysts since 30.”

“I think that whether I get pancreatic cancer or not, is total out of my control. I have great faith in the workings of science and participate in the EUS to continue the search for more information.”

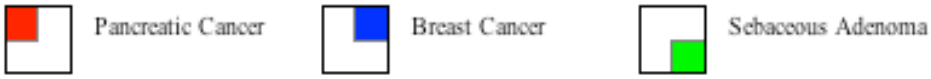
PA0469: “I have found it impossible to get my first cousins to discuss pancreatic cancer with their physicians and family. My cousins do not want to discuss this subject.”

"I've told my family how to find a doctor and what information to gather. They just don't want to [talk] about it. I don't understand it."

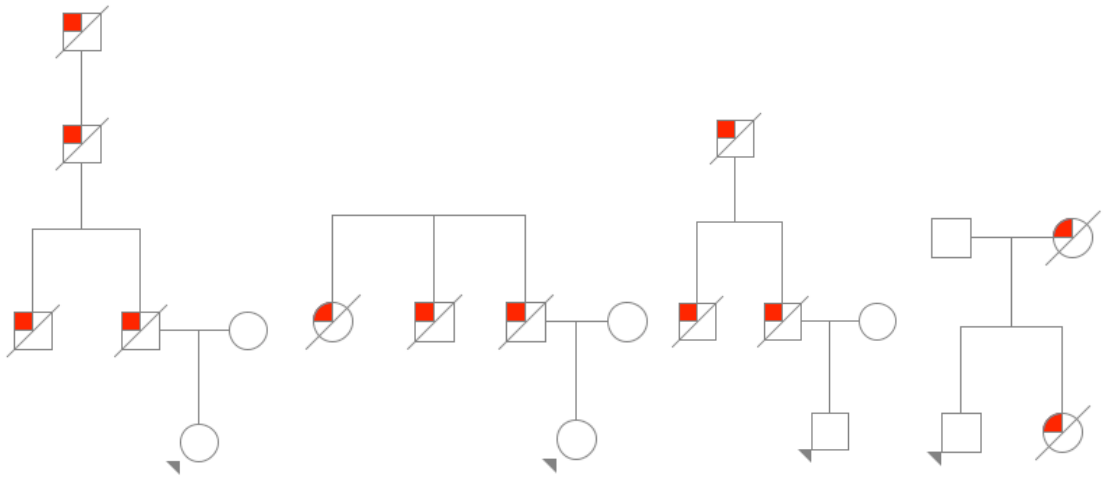
APPENDIX D

FAMILY HISTORY PEDIGREES

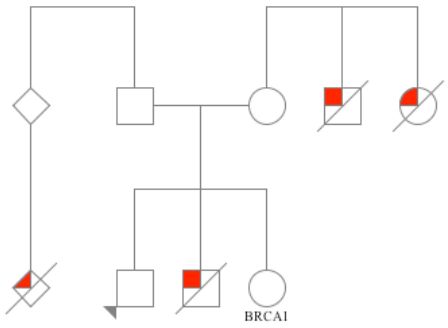
The following is a key for the pedigrees below:



PA1652 PA1324 PA0469 PA0998



PA1091



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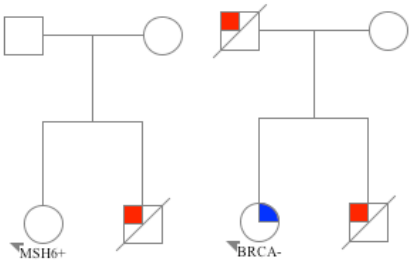

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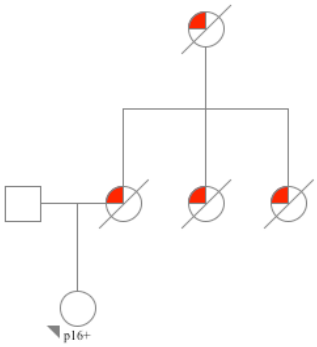

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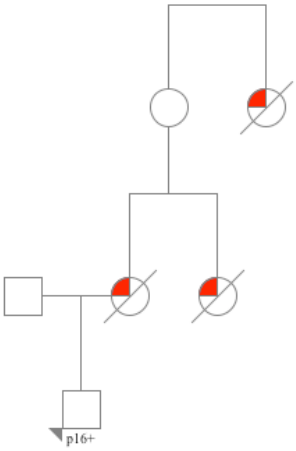

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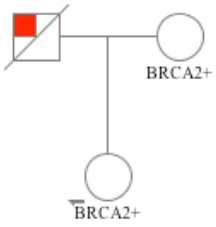

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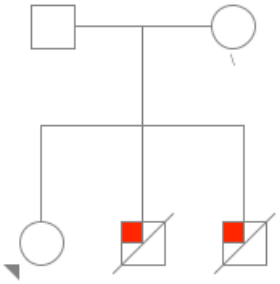

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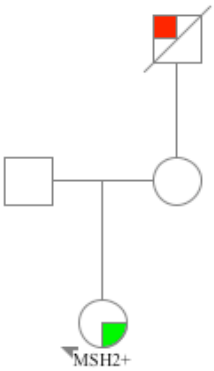

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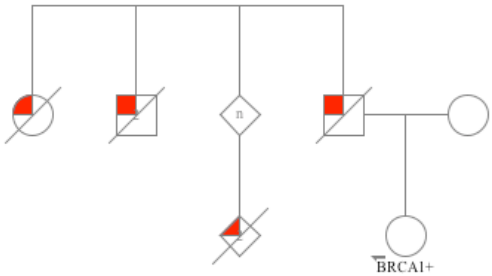

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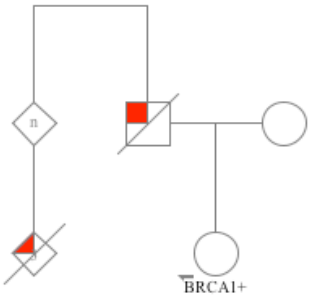

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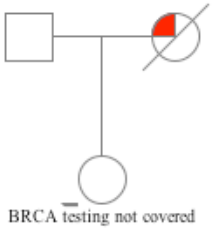

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