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Identifying high-risk patients for pancreatic cancer

Emily Therese Carbott

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Dedication

Acknowledgements

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INTRODUCTION

According to the American Cancer Society, pancreatic cancer accounts for 3% of all new cancer cases each year in the United States. A total of 43,920 new cases, 22,090 in males and 21,830 in females, are expected to be diagnosed in 2012. Pancreatic cancer has one of the worst prognoses of any type of cancer, with a 5-year survival rate of only 6%. It is estimated that 37,660 deaths are expected to occur in 2012, with 18,850 in males and 18,540 in females (American Cancer Society [ACS], 2012). Currently, there are no effective means of screening or early detection, which explains why the prognosis is poor. The lifetime risk of developing pancreatic cancer is 1 in 71 (1.41%) (ACS, 2011). In the general population the likelihood of being diagnosed with pancreatic cancer is low, but for those diagnosed with the devastating disease, the prognosis is grim.

The pancreas is located deep in the abdomen behind the stomach. It is composed of two cell types: exocrine and endocrine cells. The exocrine cells, which make up the majority of the pancreas, function by secreting enzymes that aid in digestion. Endocrine cells secrete hormones, such as insulin and glucagon, to monitor the amount of sugar in the blood. Pancreatic tumors originate from both exocrine and endocrine cells; however, each cell type forms completely different tumors (ACS, 2011). Exocrine tumors are the most common type of pancreatic cancer with about 95% of patients diagnosed with adenocarinoma originating in the exocrine glands. Endocrine tumors are much less common, making up about 5% of pancreatic tumors (American Joint Committee on Cancer, 2010). It is important to differentiate between exocrine and endocrine tumors as they vary in etiology, signs and symptoms, treatment options, and prognoses. Survival rates for pancreatic carcinoma are stage-dependent (Brand, Lerch, Rubinstein et al., 2006).

The stage of pancreatic cancer is the most important factor in choosing treatment options and predicting a patient's prognosis (ACS, 2011). Healthcare providers are able to stage pancreatic cancer two ways. The first system stages tumors as (1) resectable, (2) locally advanced, or (3) metastatic. This system classifies pancreatic tumors based on surgical resection. A resectable tumor is confined to the pancreas, and therefore, can be surgically removed. Unfortunately, only 10% to 15% of patients are diagnosed at this stage (ASCO, 2012). Those patients who do undergo resection, the 5-year survival rate ranges between 10% and 25% (Hartman & Krasinskas, 2012). Locally advanced tumors are located in the pancreas, but can't be surgically removed because it has grown into nearby arteries or veins. Approximately 35-40% of patients are diagnosed at this stage (ASCO, 2012). Metastatic tumors have spread beyond the pancreas and to other organs, making the tumor inoperable. Approximately 45-55% of patients are diagnosed at this stage (ASCO,2012). This classification system is most commonly used in pancreatic tumors since most patients do not undergo surgical resection.

The American Joint Committee on Cancer (AJCC) created the Tumor-Node-Metastasis (TNM) staging system. The TNM system contains three key pieces of information: size of the tumor, lymph node involvement, and metastasis. AJCC bases the preoperative clinical staging of pancreatic cancer on the results of high-quality cross-sectional imaging, through which local respectability and the absence or presence of distant disease is determined (Edge et al., 2010). This system is further classified into roman numerals I-IV. Stage I indicates that the tumor is confined to the pancreas, and has not spread to nearby lymph nodes. Stage II indicates the tumor is growing outside the pancreas and may have spread to nearby blood vessels. In stage III the tumor is growing outside the pancreas into nearby large blood vessels or major nerves, and it may have spread to nearby lymph nodes. Stage IV indicates the cancer has spread to distant sites

(Strosberg, Cheema & Weber, 2011). The American Cancer Society and American College of Surgeons Commission on Cancer analyzed trends for pancreatic cancer. In the report, they analyzed 44,438 patients diagnosed with pancreatic cancer between the years of 1985-1990. The data shows that among the four stages, the majority of patients (11,462) were diagnosed at Stage IV compared to Stage I (4,787), Stage II (3,031) and Stage III (4,289). The 5-year survival rate was highest for patients diagnosed in Stage I (11.9%) compared to Stage II (6.1%), Stage III (7.6%) and Stage IV (2.3%) (Sener et al.,1999). From this data, we can argue that identifying pancreatic cancer in stage I can lead to improved survival rates. It also shows how silently aggressive pancreatic cancer can be, the majority of cases are diagnosed late in the disease process making survival near impossible.

Pancreatic cancer is the fourth most deadly cancer in the United States, following lung, colorectal, and breast cancer. The mortality rate is nearly identical to the incidence rate, highlighting the poor prognosis of this disease (Rulyak et al., 2003). Multiple factors can explain why this disease is so deadly. One factor is the inability of healthcare providers to diagnose the disease at an early stage. Patients are often asymptomatic, and the location of the pancreas does not allow tumors to be seen or felt on physical exam (ACS, 2012). In addition, there currently are no screening guidelines in place to identify potential precursor lesions in patients. Lastly, the current therapies available for treatment show the best survival rates when the disease is treated in stage one.

With limited therapeutic options available at this time to cure pancreatic cancer or to substantially prolong survival, understanding the risk factors and identifying people at high risk are critical to the prevention of this disease (Schenk et al., 2001). The incidence rate for pancreatic cancer is low; therefore it is not feasible to screen the entire population (Brand et al.,

2006). This review will identify patients at high risk for pancreatic cancer, and explain the importance of screening these individuals before symptoms appear. By detecting pancreatic lesions at an early stage the five-year survival rate can be increased and give hope to patients diagnosed with pancreatic cancer.

FAMILY HISTORY

A family medical history consistently serves as a superior tool for predicting an individual's risk of developing certain diseases (American Society of Human Genetics, 2010). Approximately 5–10% of pancreatic carcinoma patients report a family history of the disease (McWilliams et al., 2005). Familial pancreatic cancer is defined as two or more first-degree relatives (brothers, sisters, parents and children) with pancreatic cancer or one first-degree relative who developed pancreatic cancer before the age of 50 (Klein et al., 2004). A number of population-based, case-control studies, and cohort studies have shown a family history of pancreatic cancer to be a risk factor for the development of pancreatic cancer.

The National Familial Pancreas Tumor Registry (NFPTR) is one of the largest registries of familial pancreatic cancer in the world. This registry recruits patients from The Johns Hopkins Hospital and individuals referred by non-Johns Hopkins physicians, nurses, or genetic counselors. A total of 5,179 individuals from 838 kindreds were analyzed. At the start of the study 3,904 of these individuals had a first-degree relative with pancreatic cancer, 906 had a more distant relative with pancreatic cancer. Among the familial pancreatic cancer kindred members, the risk of pancreatic cancer increased as their number of first-degree relatives with pancreatic cancer increased. Familial pancreatic cancer kindred study participants having three or more affected first-degree relatives had a 32.0-fold increased risk of developing pancreatic cancer (95% CI, 10.4–74.7). Those with two-affected first-degree relatives with pancreatic cancer had a 6.4-fold increased risk (95% CI, 1.8–16.4), whereas those with a single affected first-degree relative had a 4.5-fold increased risk (95% CI, 0.54 –16.3) (Klein et al., 2004).

McWilliams and colleagues (2005) conducted a study with the Mayo Clinic College of Medicine where they analyzed 426 patients from the Mayo Clinic Pancreatic Cancer Patient

Registry. Each patient enrolled had been diagnosed with pancreatic cancer and completed a detailed questionnaire regarding risk factors and family history. Individuals with at least one blood relative diagnosed with pancreatic cancer were further characterized for family-based studies. In the family based-study a total of 3355 first-degree relatives from 426 patients were analyzed, which included 1372 siblings, 851 parents, and 1132 children. When analyzing parents and siblings (n=2223) the risk of pancreatic cancer was increased (Standardized incidence ratio [SIR] of 1.92; 95% CI, 1.29-2.74). This study also analyzed the age of diagnosis as a risk factor for familial pancreatic cancer. The results show that a diagnosis before the age of 60 (n=830 relatives), was found to further increase the risk of pancreatic cancer to nearly threefold (SIR of 2.86; 95% CI, 1.15-5.89) ((McWilliams et al., 2005).

Another study, performed by Coughlin and associates in 2000, 483,109 men and 619,199 females were followed for 14 years as a part of the American Cancer Society's (ACS) Cancer Prevention Study II (CPS II). One goal of this study was to identify possible risk factors for pancreatic cancer mortality, including family history of pancreatic cancer. In this large, prospective study of United States adults 3751 persons died from pancreatic cancer. The results showed men (relative risk 1.5; 95% CI, 1.1-2.1) and women (relative risk 1.7; 95% 1.3-2.3) who reported a family history of pancreatic cancer at the time of the study were found to have a higher risk of dying from pancreatic cancer. (Coughlin et al., 2000).

Routine questioning of patients about a family history of pancreatic cancer, and the age of onset may help identify individuals at high risk of pancreatic cancer (Schenk et al., 2001).

NEW ONSET TYPE 2 DIABETES MELLITUS

The correlation between diabetes mellitus (DM) and pancreatic cancer has been acknowledged for many years; patients with type 1 or type 2 DM have an increased risk for pancreatic cancer (Magruder, 2011). In the United States, the incidence of pancreatic cancer is low, but prevalence of DM is increasing drastically. The Center for Disease Control and Prevention (CDC) reports that from 1980-2010, the number of Americans diagnosed with diabetes has more than tripled from 5.6 million to 20.9 million. In 2011, The American Diabetes Association reported the number of individuals diagnosed with diabetes mellitus was 25.8 million or 8.3% of the population. The increased prevalence of diabetes in the general population may put these individuals at an increased risk of developing pancreatic cancer; therefore the need to screen for pancreatic cancer while they are asymptomatic is imperative.

It has been reported that the prevalence of diabetes and impaired glucose tolerance in pancreatic cancer cases is as high as 80% (Li, 2012). However, it is still unclear if diabetes is an etiology of pancreatic cancer, or if diabetes is a consequence of pancreatic cancer. The association between diabetes mellitus and pancreatic cancer has been evaluated in multiple studies. The majority indicates there is a positive relationship between DM and pancreatic cancer. Research is focusing on new-onset diabetes (< 24 months) versus long duration diabetes and how it correlates with pancreatic cancer.

In 1995, a meta-analysis performed by James Everhart, MD and David Wright, PhD analyzed 11 case-control studies (2,546 patients) and 9 population cohort studies (>7,000 subjects) to evaluate diabetes mellitus as a risk factor for pancreatic cancer with the consideration that diabetes may also be a consequence of pancreatic cancer. The subjects involved had to meet the criteria of at least one year of diabetes prior to the diagnosis or death from pancreatic cancer. The

pooled relative risk of pancreatic cancer for those whose diabetes was diagnosed at least one year prior to either diagnosis of pancreatic cancer or to pancreatic death was 2.1 (95% CI: 1.6-2.8) (Everhart, 1995). These values were very similar when looked at patients with a duration of diabetes mellitus for at least five years (RR 2.0 (95% CI, 1.2-3.2) (Everhart, 1995). They concluded that pancreatic cancer occurs with increased frequency among persons diagnosed with diabetes mellitus.

In a population-based cohort study out of Rochester, Minnesota involving 2,122 residents over the age of 50 who met criteria for diabetes were followed to the earliest of pancreatic cancer diagnosis, death, or up to 3 years. During this time 18 subjects (0.85%) met criteria for pancreatic cancer (Chari, 2005). Chari and associates attempted to use hyperglycemia and diabetes to define a population at risk for having pancreatic cancer. Long-standing diabetes is an etiologic factor for pancreatic cancer, and new-onset diabetes is a manifestation of the cancer (Chari, 2005). Diabetes and hyperglycemia are present in up to 80% of pancreatic cancer cases, and are usually of recent onset, and improve or remit after resection of tumor (Chari, 2005). They also found that 44% of pancreatic cancer subjects in the cohort met criteria for diabetes $\geq$ 6 months before the diagnosis of cancer (Chari, 2005). These results would suggest that patients with new-onset diabetes are at higher risk of developing pancreatic cancer, and therefore may help identify asymptomatic patients who need to be screen for pancreatic cancer.

In the most recent study performed by Chari and associates they analyzed the medical records of pancreatic cancer cases seen at Mayo Clinic between January 15, 1981 and July 9, 2004. The goal of this study was to confirm the association between pancreatic cancer and new-onset DM and determine the association of DM in pancreatic cancer compared to age- and sex-matched subjects without pancreatic cancer (Chari, 2008). Study subjects were defined as having

at least one fasting blood sugar ≥126mg/dl or they were on anti-diabetic medications. The duration from meeting diagnostic criteria was broken into 12-month intervals, ending at 60 months. The study included 736 cases and 1,875 controls. The results indicate that at any time in the 60-month period before diagnosis, a greater proportion of pancreatic subjects met criteria for DM compared to the controls (296/736 (40.2%) vs 360/1875 (19.2%), $p<0.0001$). DM was more likely to be new onset (within 24 months before diagnosis) in subjects with pancreatic cancer compared to subjects without pancreatic cancer (52.3% vs 23.6%, $p<0.0001$) (Chari, 2008).

A common limitation among the various studies is the inability to differentiate new-onset Type 2 DM vs. new-onset pancreatic cancer induced diabetes. A study conducted at the Samsung Medical Center reviewed medical records of new-onset diabetes cases from August 2003 to May 2009. Diagnosis of diabetes was based on the American Diabetes Association criteria, and new-onset was defined as a diagnosis within 2 years. The case group consisted of 151 patients with new-onset diabetes and pancreatic cancer who were diagnosed by surgery or biopsy. The control group consisted of 302 patients with new-onset diabetes without an earlier history of cancer. In addition, they reviewed age, sex, weight change, BMI, family history of DM, and tobacco use. They found that among new-onset diabetic patients, those who were elderly (>65 years old), had no family history of DM, weight loss, and had lower BMI were more likely to develop pancreatic cancer. This study suggests a way to limit the amount of new-onset diabetic patients to a narrower and more high-risk group.

In view of the modest association between long standing diabetes and pancreatic cancer, the low incidence of pancreatic cancer, and the fact that diabetes is prevalent in the general population, screening all patients with long-standing diabetes for pancreatic cancer will not be cost effective (Pannala, 2009). However, there is an association between the two diagnoses so

we can add new-onset diabetes caused by cancer seems to be a clinically useful marker of asymptomatic, early-stage pancreatic cancer.

HEREDITARY PANCREATIC CANCER SYNDROMES

Gene mutations are abnormal copies of certain genes that can be passed from parent to child. These inherited abnormal genes may cause as many as 10% of pancreatic cancers (American Cancer Society, 2012). There is a wide spectrum of genetic variation involved in pancreatic cancer. On one end of the spectrum there is a rare genetic variation that is associated with a very high lifetime risk of developing diseases, high penetrance genes (Klein, 2012). The opposite end of the spectrum involves common genetic variation with a minor increase risk of disease, low penetrance genes (Klein, 2012). The mutations identified as high penetrance genes associated with pancreatic cancer are: mutations in *p16/CDKN2A* (Familial atypical multiple mole melanoma), *STK11* (Peutz-Jeghers syndrome), *PRSS1* (Hereditary pancreatitis), and *BRCA2* (breast and ovarian cancer predisposition gene). These mutations are also known as hereditary pancreatic cancer syndromes.

Germline mutations in the p16/CDKN2A gene are most commonly associated with familial atypical multiple mole melanoma (FAMMM). FAMMM is an autosomal dominant inherited syndrome characterized by multiple nevi, atypical nevi, and multiple melanomas (Mize et al., 2009). Recent studies have shown that the p16 mutation associated with FAMMM is also associated with an increased risk of pancreatic cancer. Lynch and colleagues followed eight families with FAMMM, and they identified a 13-22 fold increased risk of developing pancreatic cancer. The lifetime risk in individuals who carry p16 mutation was estimated to be 17% by the age of 75 (Lynch, 2008). Similarly, de Snoo and colleagues studied 22 families with the p16-Leiden founder mutation. In this study they were analyzing the risk of cancers other than melanoma in melanoma families positive for the p16-Leiden mutation. Their analysis found that

carriers of the mutation have a 47-fold increased risk of developing pancreatic cancer (RR46.6, 95% CI 24.7-76.4).

Peutz-Jeghers syndrome is an autosomal dominate syndrome characterized by melanocytic macules on the lips and buccal mucosa, and hamartomatous polyps of the gastrointestinal tract. (Giardiello, 2000). The germline mutation that accounts for this syndrome is STK11 gene. Individuals with Peutz-Jeghers syndrome have an increased risk of several gastrointestinal cancers, with an overall lifetime risk of cancer of 93%. (Klein, 2012). Hearle and colleagues (2006) reported that 80% of STK11 mutation carriers develop some form of cancer by the age of 60 years old. Specifically, their risk of developing pancreatic cancer by the age of sixty years old is 33%. Giardiello and colleagues examined 210 individuals with Peutz-Jeghers syndrome and reported a 132-fold (95% CI44-261) relative risk and a cumulative lifetime risk of 36% for the development of pancreatic cancer. (Giardiello, 2000*).* The high risk of developing pancreatic cancer in patients with Peutz-Jeghers syndrome shows the clinical importance of developing an effective screening tool for pancreatic cancer in high-risk patients.

Mutations in BRCA2 have been associated with an increased risk of breast, ovarian, prostate and pancreatic cancer (Klein,2004). Analysis of a large series of BRCA2 mutation positive families ascertained for young onset breast and/or ovarian cancer estimated that BRCA2 mutations carriers have a 3.5-fold (95% CI 1.9-6.6) increased risk of pancreatic cancer compared with non-carriers (Breast Cancer linkage consortium). A study conducted at The Johns Hopkins Medical Institution and The Mayo Clinic analyzed DNA from pancreatic cancer patients from well-defined pancreatic cancer kindreds in whom three or more members were affected with pancreatic cancer. Hahn and colleagues reported a 12% of patients from familial pancreatic cancer kindreds had deleterious BRCA2 mutations. (Hahn, 2003).

Hereditary pancreatitis is inherited as an autosomal dominant trait, with majority of cases linked to the PRSS1 mutation. Hereditary pancreatitis is characterized by recurrent episodes of severe acute pancreatitis starting at a young age (Gorry, 1997). Most patients ultimately develop chronic pancreatitis. There is a high incidence of pancreatic cancer 30-40 years after the age of onset of recurrent attacks of pancreatitis (Gorry, 1997). Lowenfels and colleagues (1997) performed a longitudinal study to assess the frequency of pancreatic cancer and other others tumors in patients with hereditary form of pancreatitis. The study included 246 patients, of which 8 were later diagnosed with pancreatic cancer. They concluded that individuals with hereditary pancreatitis have been shown to have a 53-fold (95% CI23-105) increased risk for developing pancreatic cancer and a lifetime risk of pancreatic cancer of 30-40% (Lowenfels, 1997). For the eight patients who developed pancreatic cancer, the mean age (+/-SD) at onset of pancreatic cancer was 56.9 +/- 11.2 years, and the mean number of years from onset of symptoms of pancreatitis until diagnosis of pancreatic cancer was 39.6 +/- 9.7 years (Lowenfels, 1997). Lowenvels added that the risk is even higher among smokers with hereditary pancreatitis who tend to develop disease 20 years before non-smokers. The high risk in patients with hereditary pancreatitis may be related to the early onset of pancreatitis, so that over a prolonged time periods, there is progression of disease, tissue destruction, and, eventually, development of defects in cellular repair.

Estimates of cancer risk associated with these inherited genetic syndromes are clinically important to help implement pancreatic cancer screening programs and development of prevention programs. There are currently several ongoing clinical trials evaluating the usefulness of screening of high-risk populations, including individuals who carry a mutation in an established high-penetrance pancreatic cancer susceptibility gene (Klein, 2012). Identifying

individuals who carry these gene mutations will allow healthcare providers to screen and detect those affected with pancreatic cancer before they become symptomatic.

CIGARETTE SMOKING

According to the National Cancer Institute, tobacco use is the leading cause of preventable illness and death in the United States. In addition to lung cancer, tobacco use has been linked to many other types of cancer, including cancers of the throat, mouth, stomach, pancreas, kidney, bladder, and cervix. The Center for Disease and Control reported that 19.3% of adults in 2010 were cigarette smokers. In terms of pancreatic cancer, it is estimated that 20%-25% of pancreatic tumors are attributable to cigarette smoking, and individuals who smoke carry more cancer-related genetic mutations than do nonsmokers (Lynch, 2009). In those with a family history of pancreatic cancer, smoking has even a greater effect; they have up to a 3.7-fold increase of developing pancreatic cancer and may present with the disease one to two decades earlier (Klein, 2004). Smoking also increases the risk for pancreatic cancer in individuals with hereditary pancreatitis by 2-fold (Lowenfels, 2001).

A study out of New York City examined the effects of cigarette smoking on pancreatic cancer in males and females. This was a large case-control study based on direct interviews with four hundred and eighty-four patients with pancreatic carcinoma and nine hundred and fifty-four control subjects who did not have pancreatic cancer, but were hospitalized for conditions not related to tobacco use. A trained interviewer questioned all participants on tobacco smoking, alcohol consumption, occupation and occupational exposures, weight, height, and medical history of illness and disease. In this study, current smoking was defined as having smoked at least one cigarette/day in the year preceding the current diagnosis. Ex-smokers were quitters who had not smoked within the past year. The risk for pancreatic cancer among current smokers was OR 1.6 (95% CI, 1.1-2.4) for men and OR 2.3 (95% CI, 1.4-3.5) for woman compared to men and women who never smoked tobacco (Muscat, 1997). The risk for pancreatic cancer

increased when the researchers analyzed the number of cigarettes smoked per day. For participants who smoked 20-30 cigarettes per day the OR was 1.4 (95%CI, 0.7-2.8) in men and 2.3 (95% CI, 0.8-3.6) in women (Muscat, 1997). For two or more packs/day, the OR was 1.8 (95% CI, 0.9-3.6) in men and 5.6 (95%CI, 2.0-15.8) in women. (Muscat, 1997). The authors also analyzed the duration of tobacco use, and they also confirmed an increased risk of pancreatic cancer with increasing duration of use. Male patients who smoked forty or more years had a 1.3(95%CI, 0.8-2.1 fold risk of pancreatic cancer, compared to a 2.1(95% CI, 1.3-3.4) fold risk for women (Muscat, 1997).

According to the CDC, the trend for cigarette smokers in the United States is declining (19.3%). However, it would not be cost effective to screen each of these individuals for pancreatic cancer. Based on this studies findings, it would be beneficial to screen current smokers who smoke more than 20 cigarettes/day or those with a long smoking history.

A meta-analysis performed by Lynch and associates analyzed the risk of pancreatic cancer in relation to cigarette smoking, specifically analyzing smoking intensity, duration, and pack-years. The authors used pooled data from the international Pancreatic Cancer Cohort Consortium that totaled 1,481 cases and 1,539 controls. The Pancreatic Cancer Cohort Consortium is an international initiative that includes investigators from 12 prospective epidemiologic cohorts and one case-control study to identify genetic markers of susceptibility through a genome-wide association study and to investigate environmental and lifestyle risk factors for pancreatic cancer (Lynch, 2009). Participants were classified into different groups based on their cigarette smoking history. The classifications were identified as ever smokers, former smokers, and never smokers. The ever smokers group included participants that had ever smoked, smoked over 100 cigarettes in a lifetime, or if they smoked cigarettes for six months or

longer. Former smokers were defined as those who reported stopping smoking on the most recent questionnaire prior to their diagnosis of pancreatic cancer.

The ever smokers group were further categorized by age at which they began smoking, current smoking habits, intensity and duration of smoking. Their results showed that compared with never smokers, current smokers had a statistically significant increased risk of pancreatic cancer (OR=1.77, 95% CI, 1.38,2.26), whereas former smokers had a non-significant risk (OR=1.09, 95% CI: 091,1.30)(Lynch, 2009). Pancreatic cancer risk increased significantly in smokers with increasing intensity (>30 cigarettes/day OR=1.75, 95% CI:1.27,2.42), duration (>50 years: OR=2.13, 95% CI: 1.25,3.62) and pack-years (>40 pack-years: OR=1.78, 95% CI: 1.35,2.34)(Lynch 2009). However, the age when participants started smoking was not associated with an increased risk of pancreatic cancer.

The results in this meta-analysis show that current smokers, compared with never smokers, have about an 80% increased risk of pancreatic cancer (Lynch, 2009). The results obtained by Lynch and associates are similar to the findings observed by Muscart and associates.

Another study analyzed the effect of smoking on the age at diagnosis of pancreatic cancer. This study gathered information from two separate data sources. IMPAC Services, Inc Cancer Information Resource File (CIRF) incorporates cancer patient data from more than 350 hospitals nationwide. The second database was out of the University of Michigan Pancreatic Cancer Registry (UMPCR) and included all patients with confirmed pancreatic adenocarcinoma who were seen at the University of Michigan. In the CIRF database, current smokers were diagnosed at 62.8 years old (+/-11.3) compared to never smokers who were diagnosed at 71.2 years old (+/- 11.9). The UMPCR database diagnosed current smokers at 58.1 years old (+/- 10.0) compared to never smokers 64.4 years old (+/- 12.3). The results of this study showed that current cigarette

smokers were diagnosed at significantly younger ages than never smokers, according to data from the CIRF and UMPCR (8.3 and 6.3 years earlier, respectively). This study helps support the idea of early screening for pancreatic cancer. According to the Surveillance Epidemiology End Results data stats that 68.6% of all cases are diagnosed at age 65 or older. This study provides evidence that current cigarette smoking substantially reduces the age at pancreatic cancer diagnosis in the general public (Brand, 2009).

CONCLUSION

Pancreatic cancer is the fourth leading cause of cancer death in the United States, with a poor 5-year survival rate of less than 5%. Despite advancements in screening and early detection of other cancers such as breast and colon cancer, no reliable screening test exists for pancreatic cancer.

An ideal pancreatic cancer-screening test should be a safe, inexpensive, and accurate test that reliably diagnoses pancreatic cancer at a state when it is not causing symptoms. Since these tools do not exist, we need to identify individuals at higher risk for pancreatic cancer, so we can begin screening these patients. Two benefits can come from this approach. First, we can identify early cancer lesions in high-risk patients, and also we can test various screening tools to find which tests are sensitive and specific for pancreatic cancer.

This literature review identified individuals considered high-risk for developing pancreatic cancer. Research has shown that individuals with abnormalities in certain genes, such as BRCA2, p16, STK11, PRSS1 and a family history are all predisposed to pancreatic cancer. These individuals are at high-risk of developing pancreatic cancer, and therefore, should undergo screening tests to monitor for the onset of precursor lesions. Secondly, changes in the pancreas cells can give rise to cancer. Most of these changes are not inherited and occur as the result of factors such as new-onset diabetes, increasing age and cigarette smoking.

Current literature and researchers admit there is a need to create a screening method for this disease, however there is no consensus on who to screen, how to screen, how frequently to screen, and what to do with the findings.

With the current emphasis on identifying risk factors, it is hoped that in the near future, specific and sensitive screening tests will be developed. Specifically a screening test that will be

able to detect pancreatic cancer before symptoms appear, and while it can be cured. As healthcare providers it is imperative to routinely explore the family and social history of each of our patients to recognize the risk factors associated with pancreatic cancer. Appropriate screening, early detection, and effective treatment options may lead to a more hopeful prognosis in patients with pancreatic cancer.

References

American Cancer Society. (2011, Dec. 1). Pancreatic cancer. Retrieved 01/09/2012, from http://www.cancer.org

American Cancer Society. (2012). Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society; 2012.

American Joint Committee on Cancer. Exocrine and Endocrine Pancreas. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010:241-246.

American Society of Clinical Oncology. (2012). Pancreatic Cancer. Retrieved January 16, 2012, from http://www.cancer.net.

American Society of Human Genetics. (2010). New research validates clinical use of family health history as the 'gold standard' for assessing personal disease risk. Retrieved January 16, 2012, from http://www.ashg.org.

Brand, R. E., Lerch, M.M., Rubinstein, W.S., Neoptolemos, J.P., et al. (2006). Advances in counseling and surveillance of patents at risk for pancreatic cancer. *Journal of Gastroenterology and Hepatology,* 56(10), 1460-9.

Brand, R.E., Greer, J.B., Zolotaevsky, E., Brand, R., Du, H.,& Simeone, D. (2009). Pancreatic cancer patients who smoke and drink are diagnosed at younger ages. *Clinical Gastroenteroloy and Hepatology, 7,* 1007-1012.

Center for Disease Control and Prevention. (2011). 2011 National diabetes fact sheet. Retrieved May 10, 2012. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

Coughlin, S.S., Calle, E.E., Patel, A.V. & Thun, M.J. (2000). Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes and Control, 11,* 915-923.

Edge, S.B., Byrd, D.R., & Compton, C.C. (2010). Exocrine and endocrine pancreas. *AJCC Cancer Staging Manual. 7,* 241-249.

Fremgen, A., Mencky, H.R., Sener, S., Winchester, D.P.(1999). Pancreatic Cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995. *Journal of American College of Surgeons,* 189(1).

Chari, ST., Leibson, C.L., Rabe, K.G., et al. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. *Gastroenterology.* 2005;129(2):504-511.

Chari, S.T., Leibson, C.L., Rabe, K.G., Timmons, L.J., Ransom, J., DeAndrade, M., & Petersen, G.M. (2008). Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology.* 134(1): 95-101.

De Snoo, F.A., Bishop, D.T. & Bergman, W. (2008). Increased risk of cancer other than melanoma in CDKN2A found mutation (p16-Leiden)-positive melanoma families. *Clinical Cancer Research, 14,* 7151-7157.

Everhart, J., Wright, D. Diabetes mellitus as a risk factor for pancreatic cancer: a meta analysis. *JAMA*. 1995; 273:1605-1609.

Giardiello, F.M., Brensinger, J.D., Tersmette, A.C., Goodman, S.N., Petersen, G.M., Booker, S.V., Cruz-Correa, M., & Offerhause, J.A. (2000). Very high risk of cancer in familial peutz-jeghers syndrome. *Gastroenterology, 119,* 1447-1453.

Gorry, M.C., Gabbaizedeh, D., Furey, W., Gates, L.K., Preston, R.A., & Aston, C.E. (1997). Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology, 113,* 1063-1068.

Hartman, D.J., Krasinskas, A.M. (2012). Assessing treatment effect in pancreatic cancer. *Archives of Pathology & Laboratory Medicine.* 136.

Hahn, S.A., Greenhalf, B., Ellis, I., Sina-Frey, M., Rieder, H., & Korte, B. (2003). BRCA2 germline mutations in familial pancreatic carcinoma. *Journal of the National Cancer Institute.* 95(3); 214-221.

Klein, Alison P. (2012). Genetic susceptibility to pancreatic cancer. *Molecular Carcinogenesis, 51,* 14-24.

Klein, A.P., Brune, K.A., & Petersen, G.M. (2004). Prospective risk of pancreatic cancer in familial cancer kindreds. *Cancer Research*. *64;* 2634-2638.

Li, Donghui. (2012). Diabetes and pancreatic cancer. *Molecular Carcinogenesis, 51,* 64 74.

Lowenfels, A.B., Maisonneuve, P., DiMagno, E.P., Elitsur, Y., Gates, L.K., & Perrault, J. (1997). Hereditary pancreatitis and the risk of pancreatic cancer. *Journal of the National Cancer Institute.* 89(6); 442- 446.

Lowenfels, A.B., Maisonneuve, P., & Whitcomb, D.C. (2001). Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *JAMA.* 286; 169-170.

Lynch, H.T., Fusaro, R.M., Lynch, J.F. & Brand, R.(2008). Pancreatic cancer and the FAMMM syndrome. *Familial Cancer, 7,* 103-112.

Lynch, S.M., Vrieling, A., Lubin, J.H., Kraft,P., Mendelsohn, J.B., Hartge, P. & Canzian, F. (2009). Cigarette smoking and pancreatic cancer: a pooled analysis form the pancreatic cancer cohort consortium. *American Journal of Epidemiology.* 170(4); 403-413.

Magruder, J.T., Elahi, D., & Andersen, D. Diabetes and pancreatic cancer: chicken or egg? *Pancreas.* 2011; 40(3):339-351.

McWilliams, R.R., Rabe, K.G., Olswold, C., DeAndrade, M., & Petersen, G.M. (2005). Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. *Cancer*. 104(2); 388-394.

Mize, D.E., Bishop, M., Reese, E., & Sluzevich, J. (2009). Familial atypical multiple mole melanoma syndrome. *Cancer Syndromes.* http://www.ncbi.nlm.nih.gov/books/NBK7030/

Muscat, J.E., Stellamn, S.D., Hoffmann, D., & Wynder, E.L. (1997). Smoking and pancreatic cancer in men and women. *Cancer Epidemiology, Biomarkers & Prevention, 6,* 15-19.

National Cancer Institute. (2012). Cigarette smoking. Retrieved August 8, 2012 from http://www.cancer.gov/cancertopics/tobacco/smoking.

Pannala, R., Basu, A., Petersen, G.M., & Chari, S.T. (2009). New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncology, 10,* 88-95.

Rulyak, S.J., Lowenfels, A.B., Maisonneuve, P., & Brentanall, T.A. (2003). Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. *Gastroenterology.* 124:1292-1299.

Schenk, M., Schwartz, A.G., O'Neal, E., Kinnard, M., Greenson, J.K., Fryzek, J.P., Ying, G.S., & Garabrant, D.H. (2001). Familial risk of pancreatic cancer. *Journal of the National Cancer Institute.* 93(8); 640-644.

Sener, S., Fremgen, A., Menck, H., & Winchester, D. (1999). Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the national cancer database. *Journal of the American College of Surgeons.* 189(1); 1-7.

Silverman, Debra. Risk factors for pancreatic cancer: A case-control study based on direct interviews. *Teratogenesis, Carcinogeneis, and Mutagenenisis*. 2001; 21:7-25.

Strosberg, J.R., Cheema, A.,Weber, J., et al. (2011). Prognostic validity of a novel American joint committee on cancer staging classification for pancreatic neuroendocrine tumors. *Clinical Oncology*. 29(22); 3044- 3049.

ABSTRACT

OBJECTIVE: The purpose of this literature review is to identify individuals at high-risk for developing pancreatic cancer and show the importance of screening these individuals for pancreatic cancer in hopes of detecting the disease at an early stage. METHOD: The words used for the search engines were “pancreatic cancer”, “epidemiology of pancreatic cancer”, “screening methods”, “symptoms of pancreatic cancer” “high-risk individuals for pancreatic cancer”, “early detection”, “inherited genes”, “familial pancreatic cancer”, “diabetes”, “cigarette smoking”. The main search engines were MEDLINE, PubMed, Mesh, JAAAPA, American Cancer Society, National Cancer Institute, Center for Disease Control and Prevention, Gastroenterology. RESULTS: Individuals at high risk for developing pancreatic cancer are those with a family history of pancreatic cancer, new-onset diabetes, hereditary pancreatic cancer syndromes, and cigarette smoking. CONCLUSION: There are individuals that are high-risk for pancreatic cancer. There is a need to develop screening methods to identify these individuals early in the disease process.