Pancreatic Cancer and the Family Connection: The Role of Advanced Practitioners in Screening and Educating Genetically At-Risk Individuals

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Abstract

Pancreatic cancer is the third leading cause of cancer deaths in the United States. It has a 95% mortality rate within 5 years of the initial diagnosis. Pancreatic ductal adenocarcinoma is the most commonly diagnosed histotype. The average age at diagnosis is 70 years. Familial forms of pancreatic cancer have been associated with pathogenic variants in predisposing genes, including *ATM*, *BRCA1*, *BRCA2*, *PALB2*, *CDKN2A*, *STK11*, *MLH1*, and *MSH2*. Collecting information on the patient's family history may serve as a primary tool to screen an individual's risk for familial pancreatic cancer. More advanced screening options for individuals at risk include endoscopic ultrasonography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography. Due to pancreatic cancer's high mortality rate, routine screening of individuals at risk for developing familial pancreatic cancer may result in early diagnosis and improved survivability. This review aims to characterize the genetic risk factors associated with pancreatic cancer and recognize available screening options for at-risk individuals.

Pancreatic cancer is one of the deadliest cancers in the United States, accounting for 8% of cancer deaths each year. It is surpassed only by lung cancer (23%) and colorectal cancer (9%) in terms of causes of cancer deaths annually (Centers for Disease Control and Prevention [CDC], 2022). Pancreatic cancer affects approximately 89,234 individuals annually, with an estimated mortality rate of 95% within 5 years of diagnosis (National Cancer Institute, 2023; Underhill et al., 2015).

The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC; Yurgelun et al., 2018), which accounts for almost 90% of all cases (Orth et al.,

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2019). Pancreatic ductal adenocarcinoma develops in the exocrine regions of the pancreas, with the majority of tumors (approximately 65%) developing in the head of the pancreas (Sarantis et al., 2020). Histopathologic classification of pancreatic cancer is determined by microscopic exam (Collisson et al., 2019). Other rare types of exocrine pancreatic cancers account for less than 10% of pancreatic cases. These include acinar cell carcinoma (ACC), which can produce excess lipase, and mucinous cystic neoplasm (MCN) with an invasive form of adenocarcinoma. Mucinous cystic neoplasm with invasive adenocarcinoma presents as a fluid-filled cyst usually on the tail of the pancreas.

A different type of pancreatic cancer is the slow-growing pancreatic neuroendocrine tumors (NETs). These arise from the endocrine tissues of the pancreas, and they are categorized based on the hormone they produce. Pancreatic NETs can produce insulin (most common presentation), glucagon, gastrin, somatostatin, vasoactive intestinal peptide, and adrenocorticotropic hormone (American Cancer Society, 2020a). These developing tumors are often asymptomatic in early stages (Collisson et al., 2019; Pancreatic Cancer Action Network, n.d.).

Pancreatic ductal adenocarcinoma, ACC, and MCN are all associated with genetically inherited germline variants predisposing the individual to develop pancreatic cancer (Ardeshna et al., 2022; Kryklyva et al., 2019). A germline variant, or mutation, is a change in the deoxyribonucleic acid (DNA) sequence of a gene carried in either sperm or egg cells; therefore, this mutation is passed on to all offspring (National Cancer Institute, n.d.). Pancreatic NETs are typically sporadic in nature; however, 10% of these cancers are associated with autosomal dominant inherited multiple endocrine neoplasia type 1 (National Center for Advancing Translational Sciences, 2021). Unlike other gastrointestinal cancers, such as colorectal cancer, routine screening recommendations have only come to the forefront in the past decade, with the most recent recommendations being established in 2020 (Goggins et al., 2020). As a result of the lack of early symptoms and limited screening recommendations, pancreatic cancer is often detected at later stages, resulting in poorer patient outcomes. The primary aim of screening at-risk individuals is to decrease mortality from pancreatic cancer through early identification of precancerous lesions (Goggins et al., 2020).

The lack of screening options is especially problematic for individuals with a history of familial pancreatic cancer (FPC). Familial pancreatic cancer is diagnosed in individuals with two or more first-degree relatives or three or more relatives of any degree diagnosed with pancreatic cancer. Many cases of FPC are related to pathogenic variants in specific genes that are transmitted through families (Underhill et al., 2015). Out of the estimated 60,000 newly diagnosed cases of pancreatic cancer each year, approximately 10% of those are genetically susceptible forms of FPC (Hu et al., 2018).

There are several gene variants associated with an increased risk for FPC. Genes commonly affected by pathogenic variants associated with FPC include *ATM*, *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A*, while other genes such as *STK11*, *MLH1*, and *MSH2* have been less commonly associated with FPC susceptibility (Goggins et al., 2020). Pathogenic variants are genetic changes or mutations that increase an individual's susceptibility to developing certain diseases. Many pathogenic variants are associated with other familial cancer syndromes such as hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*), Lynch syndrome (*MLH1* and *MSH2*), and Peutz-Jeghers syndrome (*STK11*; American Cancer Society, 2020b). Routine genetic testing for these pathogenic variants is important for those at risk of developing FPC (Llach et al., 2020). Collecting anamnestic information on the family history and performing genetic testing are valuable procedures of screening protocols. This review aims to characterize genetic risk factors associated with FPC, specifically PDAC, and recognize current screening options that may benefit at-risk individuals.

METHODS

A literature search was conducted using several online databases, including Cumulative Index to Nursing and Allied Health Literature, MEDLINE, PubMed, and Google Scholar. Specific keywords used to research this literature topic

included "pancreatic cancer," "familial," "inherited," "genes," and "screening." All articles were published between January 2010 and October 2022, written in English, and chosen based on their relevance to the topic. This scoping review also includes information from online websites. Websites were evaluated for publishing institution, affiliation, reliability, credibility, and accuracy. Only websites with a .gov or .org URL were included.

DISCUSSION

Individuals with a family history of pancreatic cancer in two or more first-degree relatives or three or more relatives of any degree have anywhere from a 3.5% to 40% greater chance of developing pancreatic cancer than the general population (CDC, 2022). One of the main genetic components of FPC is germline variants that increase inherited susceptibility (Cancer.Net, 2021; Pancreatic Cancer Action Network, n.d.). Eighty-two percent of individuals with pathogenic variants in genes predisposing to FPC have a family history of other cancers as well (Shindo et al., 2017). Researchers discovered that 17.8% of known pathogenic variants are found in individuals with a family history of pancreatic cancer (Hu et al., 2018). This strong correlation between variants and FPC demonstrates the importance of genetic testing in individuals with a strong family history of the disease.

Because pancreatic cancer has such a high mortality rate, researchers are looking for ways to increase survivability. One way to potentially improve the survival rate is through early screening and surveillance to detect pancreatic changes at earlier stages. Pancreatic cancer is staged using the American Joint Committee on Cancer TNM System (American Cancer Society, 2017). This system rates the pathologic stage by assessing tumor size, lymph node involvement, and if any metastasis is present. The earliest stage of identification is Tis (tumor in situ), N0 (no lymph node involvement), and M0 (no metastasis). As tumor size and lymph node involvement increase, the staging of the cancer increases (American Cancer Society, 2017). Pancreatic cancer is rarely detected at an early stage, with 80% of cases diagnosed after a regional invasion or distant metastasis due to a lack of signs and symptoms until the cancer has progressed to later stages (Kim et al., 2014). Therefore, individuals at increased risk for pancreatic cancer based on family history or identifiable genetic predisposition should be prioritized and selectively screened to increase detection yield. The risk is estimated to be 6.4-fold greater in individuals with two first-degree relatives with pancreatic cancer and 32-fold greater in individuals with three or more first-degree relatives with pancreatic cancer (Canto et al., 2013).

Pathogenic Variants in Familial Pancreatic Cancer

Pathogenic germline variants have been identified in several genes associated with an increased risk of pancreatic cancer: *ATM*, *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A*. *ATM* germline variants are the most frequently seen variants in pancreatic cancer diagnoses. *ATM* variants are found in up to 10% of all PDAC cases (Yurgelun et al., 2018). *BRCA1* and *BRCA2* germline variants have been identified in 1% and 5% to 10% of PDACs, respectively (Pilarski, 2019). Additionally, pathogenic variants in *BRCA2* are associated with an earlier age of diagnosis for pancreatic cancer than seen in individuals with somatic cell changes (Hu et al., 2018). Somatic cell changes or mutations occur in body cells, other than sperm and egg cells, over the course of an individual's lifetime. It is estimated that 5% to 9% of PDAC diagnoses are associated with a germline variant in *PALB2* (Principe, 2022). *CDKN2A* variants were found to yield the highest risks of pancreatic cancer, but they were seen much less frequently (0.33%) than *ATM* (10%) and *BRCA2* (5%–10%) variants (Pilarski, 2019).

ATM

ATM is a tumor suppressor gene encoding the ATM serine/threonine protein kinase. Proteins of the ATM family are involved in DNA damage repair and cell cycle checkpoint activation in response to DNA damage; therefore, they play a critical role in maintaining genomic integrity (Armstrong et al., 2019; Kim et al., 2014). *ATM* variants give rise to catalytically inactive ATM proteins. This affects the capacity of the protein to repair DNA and hinders its ability to control cellular proliferation. With the combination of an inability to repair DNA and uncontrolled cellular proliferation, there is an increased risk of cancer

growth and metastasis. Additionally, *ATM* loss has been shown to be associated with significantly decreased overall survival in patients whose cancer had normal *TP53* expression and was a significant independent predictor of decreased overall survival (Kim et al., 2014).

The loss of tumoral *ATM* expression was significantly more common in pancreatic cancer in individuals with a family history of pancreatic cancer than in those without. *ATM* variants were detected in 24.5% of people with FPC, compared with only 11% of those without a family history of pancreatic cancer (Kim et al., 2014). The higher prevalence of tumoral loss of ATM protein in cases with a family history of pancreatic cancer suggests there may be differences in the prevalence of cancer-associated variants in familial compared with sporadic pancreatic cancer (Armstrong et al., 2019; Kim et al., 2014).

BRCA1, *BRCA2*, and *PALB2*

BRCA1 and *BRCA2* are tumor suppressor genes encoding for proteins that regulate the pace of cellular division, repair DNA damage, and suppress tumor growth. *BRCA1* and *BRCA2* variants result in the cells' inability to repair damaged DNA and inhibit tumor growth (Zhen et al., 2015). Individuals with a germline variant in *BRCA2* have a higher risk of FPC than those carrying *BRCA1* variants (Pilarski, 2019). In addition, genetically inherited mutations or variants in *BRCA1* and *BRCA2* are associated with hereditary breast and ovarian cancer. *PALB2* encodes a protein that is involved in the binding of the *BRCA2* protein. *PALB2* functions as a tumor suppressor and helps maintain genome integrity (Wu et al., 2020).

CDKN2A

CDKN2A encodes the p16 protein, a cell-cycle regulator that inhibits cyclins and serves as an important tumor suppressor (Chan et al., 2021; Zhen et al., 2015). Germline *CDKN2A* variants also predispose to early-onset melanoma. Increased risk for pancreatic cancer development has been observed in cases of *CDKN2A*-associated familial melanoma (Chan et al., 2021). When compared with FPC, sporadic cases of pancreatic cancer have a lower overall prevalence of *CDKN2A* variants (0.6%; Zhen et al., 2015).

Current Screening Options

The International Cancer of the Pancreas Screening (CAPS) Consortium met to discuss how to manage screenings for individuals at risk for pancreatic cancer. The Consortium agreed that initial screening protocols should include endoscopic ultrasonography (EUS) and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) beginning at the age of 50 years, or younger if the earliest first-degree relative was diagnosed with pancreatic cancer before the age of 50 (Goggins et al., 2020). Previous methods for pancreatic cancer screening included computed tomography (CT) scan and blood testing, but recent evidence has shown that EUS and MRI/MRCP are more effective at detecting pancreatic lesions. Additionally, it was found that MRCP provided the best visualization of cyst communication with the main pancreatic duct. Computed tomography is only recommended for individuals who are unable to undergo EUS, MRI, or MRCP (Goggins et al., 2020). Other methods for screening (ultrasound, CT scans, blood tests) are now established as substandard due to the risk of incorrect diagnosis and radiation exposure (Canto et al., 2013; Goggins et al., 2020). Although these screening techniques effectively identify pancreatic lesions, it is unclear whether they improve outcomes and survivability (Vasen et al., 2016). Additional research is needed to fill this knowledge gap.

Although EUS and MRI are both thought to be the best options for screening, they are only recommended for individuals considered to be at high risk due to the invasive nature of the tests, the use of sedatives, and the cost (Goggins et al., 2020, Konings et al., 2016). Additionally, although pancreatic cancer has one of the highest mortality rates in the United States, its prevalence is not high enough for screening to be performed on everyone. For this reason, screening is not recommended for the general public but instead for individuals at high risk, including those with a family history of pancreatic cancer and those with increased genetic susceptibility to pancreatic cancer (Goggins et al., 2020).

Pancreatic cancer surveillance aims to decrease mortality by detecting pancreatic dysplasia or tumors early. Cases of FPC have been identified

in asymptomatic patients using EUS and MRI/MRCP (Canto et al., 2018). Expert consensus is that all individuals at risk for FPC should undergo annual surveillance for early changes beginning at 50 years of age (Goggins et al., 2020). Of interest, experts disagree on whether pancreatic abnormalities of unknown significance were enough to warrant surgery. The inability of experts to reach a consensus on treatment recommendations for these types of changes presents a challenge for providers (Canto et al., 2013).

Genetic testing for germline variants is another option for high-risk individuals. Genetic testing should be offered to all individuals over the age of 18 who meet the criteria for annual surveillance due to increased pancreatic cancer risk based on family history (Goggins et al., 2020). Predictive genetic testing in children and adolescents that looks for genetic mutations linked to disease is not recommended (Biesecker, 2016). The National Comprehensive Cancer Network recommended that those with a new PDAC diagnosis undergo testing; however, the CAPS Consortium did not reach a consensus on recommending testing for newly diagnosed individuals in the absence of other risk factors (Goggins et al., 2020). There are gene panel tests to assess for the presence of known pathogenic variants associated with FPC. It is recommended that first-degree blood relatives of individuals diagnosed with FPC undergo genetic testing to exclude hereditary risks for disease development (Llach et al., 2020; Pancreatic Cancer Action Network, n.d.).

APPLICATION TO ADVANCED PRACTICE

Advanced practitioners (APs) play pivotal roles in assessing patients for disease risk factors. Advanced practitioners can complete a comprehensive patient and family history to identify disease risks. A detailed family history can pinpoint diseases across several generations and show the relationships between family members. It can indicate which individuals may express the trait in question (National Human Genome Research Institute, 2022). Another less common option for APs is to create a family pedigree. Pedigrees provide a visual depiction of disease among various generations of a family. Pedigrees contain key symbols that denote gender and relationship among individuals. Shading indicates that an individual expresses a specific phenotype (National Human Genome Research Institute, 2022). Advanced practitioners can perform pedigree analysis to identify individuals at high risk for inherited conditions, such as familial cancers. Early identification of high-risk individuals may lead to personal lifestyle changes and increased proactive disease surveillance.

While pedigree analysis is an essential aspect of risk evaluation, it does have a significant limitation: it may be challenging to perform when there is little family health history available (Son et al., 2014). Inaccurate health history can be attributed to adoption, poor historians, dishonesty, or lack of knowledge of family members. With accurate family health history, pedigrees can be a valuable tool in determining the risk an individual has of developing hereditary diseases. Tools such as pedigree analysis are important to improve patient knowledge related to pancreatic cancer risk factors and to provide holistic care.

Advanced practitioners play a vital role in patient and family education. Educating patients and families on what genetic susceptibility means and how it can impact health is important. Also, it is essential for APs to discuss the prevalence of FPC (approximately 3% to 5% of all pancreatic cancer cases) so that patients can better gauge their overall risk of disease development (Vasen et al., 2016). Advanced practitioners empower their patients and families by providing information related to available screening options and genetic tests for those at risk for pancreatic cancer.

Familial pancreatic cancer cases are a small percentage of overall pancreatic cancers in the United States; however, due to the high mortality rate of all pancreatic cancers, individuals at risk for FPC should be identified. Individuals are at higher risk for developing FPC if they have first- and second-degree relatives with pancreatic cancer (Shirts et al., 2010). Additionally, individuals with first- and second-degree female relatives diagnosed with pancreatic cancer were at greater risk for FPC when compared with individuals with male relatives diagnosed with pancreatic cancer (Kohli et al., 2018). Individuals with a family history of FPC may benefit from education about their risk factors, screening options, and available

genetic tests. Advanced practitioners can provide this education and refer to genetic specialists for further workup and counseling if an individual is identified as high risk.

CONCLUSION

Individuals at risk for FPC can benefit from routine screening to identify early signs of pancreatic cancer. Collecting a thorough family history remains the best method to identify FPC risk (Goggins et al., 2020). Performing a family history and pedigree may serve as a preliminary tool to assess an individual's risk for FPC and the need for additional screening. Genetic testing can identify a family's underlying genetic susceptibility (Llach et al., 2020). Identification of individuals at high risk for FPC is important so that health-care providers can determine effective screening strategies. Early identification and treatment of FPC may improve outcomes and survivability. Advanced practitioners play a pivotal role in identifying at-risk individuals. Performing comprehensive family histories, risk assessments, and genetic referrals for high-risk families is essential for APs. By providing quality care, APs empower their patients to be proactive and well-informed about their health. ●

Disclosure

The authors have no conflicts of interest to disclose.

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