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A Review Of Early Detection In Pancreatic Cancer

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Abstract:
Pancreatic cancer is known for being difficult to detect in its early stages. It is known to be asymptomatic until it has reached its late, and often fatal, stages. Oftentimes, a late pancreatic cancer diagnosis leads to a poor prognosis, making pancreatic cancer an incredibly deadly disease. Despite this, certain characteristics of pancreatic cancer can allow for an earlier detection. Previous research has determined several factors that can be attributed to the diagnosis of pancreatic cancer. Hereditary factors pose a considerable risk for hereditary pancreatic cancer, with various hereditary diseases being associated with the diagnosis of pancreatic cancer. Blood biomarkers, such as carbohydrate antigen 19-9 and soluble AXL, are also known to cause pancreatic cancer. In addition, certain somatic mutations in genes such as KRAS, TP53, CDKN2A, and SMAD4 additionally have a correlation with the development of pancreatic cancer. Being mindful of hereditary factors, blood biomarkers, and somatic mutations can allow for an earlier detection of pancreatic cancer. Being able to detect pancreatic cancer in its early stages is crucial for a better survival outcome.

Keywords: *pancreatic cancer, hereditary pancreatic cancer, sAXL, CA19-9, blood-based biomarkers, somatic mutations, KRAS, TP53, CDKN2A, SMAD4*

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I. Introduction

Humanity has been fighting cancer for thousands of years, yet cancer is still the leading cause of death to this date. Cancer claims hundreds of thousands of lives each year, yet researchers still lack a clear-cut solution to curing cancer. Of all the different cancer types, pancreatic cancer (PC) has one of the lowest 5-year survival rates. An estimated 227,000 people die every year from pancreatic cancer worldwide (Vincent et al., 2011). Pancreatic cancer has a poor prognosis due to having minimal symptoms in its early stages, a high rate of metastasis, minimal treatment options, and a high recurrence rate.

In its early stages, pancreatic cancer is generally asymptomatic, which means that little to no symptoms are expressed by the host. This makes pancreatic cancer relatively harder to detect, as a host has no urgent indication to check whether or not they have cancer. In fact, pancreatic cancer is usually silent until it completely invades the surrounding tissues or begins to metastasize. Pancreatic cancer additionally has a high rate of metastasis, making it much harder to treat in general. The minimal treatment options make it difficult to completely treat or remove pancreatic tumors. Even if pancreatic cancer is successfully removed for the first time, it has a high recurrence rate, which makes pancreatic cancer difficult to completely get rid of.

Many risk factors stem from pancreatic cancer. Notably, pancreatic cancer is affected by smoking history, diabetes, age, sex, and obesity. A consistent smoking history often correlates with the development of pancreatic cancer. Around 20% of pancreatic tumors are a result of a smoking history (Vincent et al., 2011). In addition, diabetes, a pancreatic disease, increases the chance for the development of pancreatic cancer. Family history is also important to consider in regards to pancreatic cancer, as 10% of reported pancreatic cancer cases include a family history (Vincent et al., 2011). The risk for pancreatic cancer dramatically increases as the level of family history increases.

Pancreatic cancer has an incredibly low survival rate because oftentimes, it is detected in its later stages. This makes it increasingly crucial to determine more indicators of pancreatic cancer in its early stages. Furthermore, pancreatic cancer therapies are limited, making it even more important to detect PC in its early stages. Some of these treatment methods include surgery, chemotherapy, and immunotherapy. However, there is only so much cancer treatments can do if PC is detected in its late stages. This literature review synthesizes various potential indicators of PC that might prove useful in improving early detection and overall survival rates.

II. Methodology

The review was composed using articles from the PubMed database. Using the keywords “pancreatic cancer”, “biomarkers”, and “somatic mutations”, a total of 265 articles were analyzed for relevance. Articles that were irrelevant, unspecific, or treatment-oriented were omitted. After a comprehensive review of 10 selected

articles, a review was written to properly synthesize each article. The inclusion criteria was composed of articles written in English published between the years 2010 and 2025.

III. Results

The content within the articles can be divided into 3 sections: hereditary pancreatic cancer, blood biomarkers, and somatic mutations. The sections explore the validity of each method as early indicators for pancreatic cancer.

Hereditary Pancreatic Cancer

Family history is an important risk factor to consider in pancreatic cancer. Around 10% of PC occurrences are thought to be caused by hereditary factors. A prospective analysis of PC occurrences determined that first-degree relatives of PC patients have a nine-fold greater risk of developing PC in their lifetime. When an individual has three or more first-degree relatives, this risk increases to 32-fold (Grover & Syngal, 2010). PC is associated with inherited cancer syndromes, such as Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma (FAMMM), and Lynch syndrome. These syndromes are a result of inherited germline mutations, in genes commonly associated with cancer development.

Peutz-Jeghers syndrome is an autosomal dominant syndrome that is caused by an inherited mutation located on chromosome 19 in the STK11 gene. PJS has a high likelihood of the development of symptoms of complications, or a high penetrance. Some of these symptoms include distinctive darker-pigmented macules, and gastrointestinal polyps that tend to develop later in life. This gene is believed to have tumor suppressor mechanisms, thus increasing the risk for cancer. PJS corresponds to an 11%-36% estimated lifetime risk for PC, affirming the hereditary relevance in PC (Grover & Syngal, 2010).

Familial atypical multiple mole melanoma is an autosomal dominant syndrome that is caused by a germline mutation in the CDKN2A gene located in chromosome 9. FAMMM has an incomplete penetrance, suggesting that the inherited mutation does not necessarily cause symptoms or complications. Symptoms include the increased occurrence of nevi (moles), which are often irregularly shaped. *CDKN2A* plays an important role in cell division, and an inherited mutation might disrupt this process from an early age. Thus, a hereditary mutation in *CDKN2A* corresponds to an increased risk of cancer. Although this risk typically causes melanomas, the risk of hereditary PC also increases with FAMMM. Individuals with FAMMM have a 13-22 fold higher risk of developing PC, further suggesting that hereditary aspects are associated with PC (Grover & Syngal, 2010).

Lynch syndrome is caused by an inherited genetic mutation in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. These genes play a crucial role in the detection and prevention of genetic mutations during DNA replication. A mutation in a mismatch repair gene indicates an increased risk of developing cancer in general. Lynch syndrome has traditionally associated with cancers of the endometrium, ovary, stomach, small bowel, urinary tract, and brain. However, recent studies suggest that Lynch syndrome corresponds to a heightened risk for PC as well. Individuals with Lynch syndrome have a 3.7% cumulative risk for PC; this risk increases to an 8.6-fold increased risk compared to the general population by the age of 70 (Grover & Syngal, 2010). However, pancreatic cancers cases that are related to Lynch syndrome are characterized by poor differentiation and microsatellite instability. These characteristics indicate weak DNA repair mechanisms. Lynch syndrome's increased risk of PC and debilitated mismatch mechanisms suggest that hereditary mutations are indeed relevant in PC.

Blood Biomarkers

Blood-based biomarkers are an emerging technology that may potentially assist in detecting, diagnosing, monitoring, and treating PC. As of now, the only FDA-approved blood-based biomarker for PC is carbohydrate antigen 19-9 (CA19-9). However, newer research suggests that soluble AXL (sAXL) might also serve as a blood-based biomarker for PC.

The traditional use of biomarkers has many limitations, often requiring a large amount of biological material to properly return results (Ceereena et al., 2023). These limitations ultimately make the traditional use of biomarkers expensive, inefficient, and laborious. However, advancements in medical technology have introduced blood-based biomarkers, which are a much cheaper and convenient alternative. The use of blood-based biomarkers is minimally invasive and can yield thousands of results from simply a few drops of blood. This novel technology carries potential uses in pancreatic cancer research, especially as blood-based biomarkers become increasingly available.

Carbohydrate antigen 19-9 is a glycoprotein and O-linked glycoprotein expressed by pancreatic cancer cells (Yang et al., 2018). An effective way to measure CA19-9 levels is through blood samples. In fact, CA19-9 levels can provide prognostic information, as patients with normal CA19-9 levels (<37 U/mL) have a prolonged median prognosis (32-36 months) compared to patients with elevated CA19-9 (>37 U/mL) levels, having a shorter median prognosis (12-15 months) (Ballehaninna & Chamberlain, 2012). In addition, CA19-9 levels of <100 U/mL

suggested that the cancer was resectable, whereas CA19-9 levels of >100 U/mL suggested that the cancer was unresectable and potentially metastatic (Ballehaninna & Chamberlain, 2012). If CA19-9 levels normalize (<37 U/mL) after resection or chemotherapy, patients will likely have a better prognosis (Ballehaninna & Chamberlain, 2012). However, CA19-9 is ultimately limited by a poor sensitivity through false positives and negatives. The overall sensitivity of CA19-9 in detecting PC in symptomatic patients is 79%-81% (Ballehaninna & Chamberlain, 2012). This limitation suggests that CA19-9 should not be definitively interpreted. Rather, it should serve as an affirmation for other variables suggesting PC.

AXL is part of the TAM family in receptor tyrosine kinases. TAM receptors play roles in cell communication, apoptotic cell clearance, and tissue repair. The TAM receptor AXL is overexpressed in 70% of pancreatic cancers (Vázquez-Bellón et al., 2024). The soluble form of AXL possess characteristics similar to that of AXL. Because sAXL is detectable in plasma, it may be increasingly relevant in PC detection and diagnosis, as it is cheaper and more convenient to assess. Increased sAXL levels were found in pancreatic cancers in the HMar cohort (n=31, median=59.78 ng/mL, IQR=25.38) and in the HClinic cohort (n=80, median=52,66 ng/mL, IQR=30.08) (Martinéz-Bosch et al., 2021).

Furthermore, the presence of elevated levels of both sAXL and CA19-9 has a higher sensitivity of 91.3% in PC and 100% in healthy controls (Vázquez-Bellón et al., 2024). This technique completely addresses the aforementioned limitation of false positives.

Somatic Mutations

One of the most common causes of cancer is somatic mutations. This is certainly true for pancreatic cancer, which is also caused by somatic mutations. A few notable genes that may cause PC when mutated are KRAS, TP53, CDKN2A, and SMAD4.

KRAS is an oncogene associated with cell proliferation. Somatic mutations in KRAS are found in ~85% of PC cases (Luo, 2021). In addition, KRAS mutations have been detected in stage 1 pancreatic intraepithelial neoplasia, a precancerous stage (Luo, 2021). This indicates that the KRAS mutation is one of the primary drivers of tumorigenesis. The prevalence of the KRAS mutation in PC indicates possible treatments by targeting the Ras pathway. However, there is little clinical success in targeting this pathway, calling for extended research.

TP53 is a tumor suppressor gene associated with apoptosis, cell cycle response, and DNA damage response (Voutsadakis, 2021). TP53 mutations are found in 60%-70% of PC cases (Luo, 2021). While p53 mutations do not play a significant role in tumorigenesis, they are associated with subsequent PC development. This provides yet another alternative pathway for PC treatment.

Although CDKN2A germline mutations are associated with hereditary PC, somatic CDKN2A mutations are equally as relevant in PC. CDKN2A is a tumor suppressor gene that regulates the cell cycle. Somatic CDKN2A mutations have been detected in more than 50% of PC cases (Luo, 2021). Similar to mutations in TP53, CDKN2A mutations often follow early KRAS mutations. Nevertheless, CDKN2A mutations provide another potential pathway to target when considering PC treatments.

SMAD4 is part of a family of transcription factors, the SMADs, but the actual role of SMAD4 is controversial (Javle et al., 2014). SMAD4 mutations are found in ~50% of PC cases, and like TP53 and CDKN2A, SMAD4 mutations follow initial KRAS mutations (Luo, 2021). In addition, an increased SMAD4 expression is associated with worse prognosis in cases involving surgical resection (Javle et al., 2014). Although less prevalent, SMAD is another gene that can be weighed regarding PC treatment.

IV. Conclusion

Although pancreatic cancer is one of the most deadly cancers, current research presents promising avenues for early detection and diagnosis. This review synthesizes various biomarkers that might assist in detecting and diagnosing PC at earlier stages. Inherited germline mutations pose various risks for PC, and some relevant diseases include Peutz-Jeghers syndrome, Familial atypical multiple mole melanoma, and Lynch syndrome. Countless sources affirm that individuals with such diseases carry a greater risk for developing PC, emphasizing the importance of frequent screenings. Blood-based biomarkers serve as a novel method for detecting and diagnosing PC in symptomatic patients. Both carbohydrate antigen 19-9 and soluble AXL have potential as valid blood biomarkers for PC. Together, these two blood biomarkers possess even greater specificity. The emerging technology surrounding blood biomarkers presents promising benefits compared to traditional biomarkers. Somatic mutations are certainly prevalent in many PC cases. Mutations in the KRAS gene occur during very early stages of PC, and mutations in TP53, CDKN2A, and SMAD4 often follow. Developing methods to improve the detection of these somatic mutations would improve early detection methods for PC. Further research should aim to determine more potential biomarkers for PC and distinguish the validity of existing PC biomarker candidates. It is important to acknowledge that some of the articles used in this review are outdated (published more than 10 years ago), specifically in hereditary pancreatic cancer and the SMAD4 somatic

mutation. Extended research on these topics could reevaluate the efficacy of these biomarkers in a modern setting, providing more accurate results.

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