Review

Early Biomarkers for Pancreatic Cancer: A Quest for Survival, Review on the Most Effective Approaches at Present

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Early Biomarkers for Pancreatic Cancer: A Quest for Survival, Review on the Most Effective Approaches at Present

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Abstract: Pancreatic cancer is the most lethal cancer, it has lowest 5-year survival rate among other types of cancers. More than half of pancreatic cancer are diagnosed at distant stage due to its insidious and non-specific symptoms. Surgery is the most effective treatment to date, but only 10-20% are resectable upon diagnosis. Currently, the only biomarker approved by the United States Food and Drug Administration (US-FDA) for pancreatic cancer is carbohydrate antigen 19-9 (CA19-9); however, it has limited use for early diagnosis. An increasing number of studies have a combination of biomarkers. Recently, the application for liquid biopsy has drawn a lot of attention, such as the use of microRNA (miRNA), circulating tumor DNA (ctDNA), and circulating tumor cells (CTC). Screening for pancreatic cancer is indicated for high-risk patients; studies of new diagnostic models combined with biomarkers for early detection also showed promising results to aid clinicians in deciding on whether to start screening. This review aims to summarize the progress on current biomarkers and new potential strategies for early detection of pancreatic cancer.

Keywords: pancreatic cancer; early biomarker; early diagnosis

1. Introduction

Pancreatic cancer is the most lethal cancer today, with the lowest 5-year survival rate among all cancers. This is estimated at 8% for all stages combined and only 3% when diagnosed at a later stage [1]. More than 50% of pancreatic cancer patients are diagnosed at a distant stage, at which point there are only limited treatment options due to the highly metastatic nature of the disease [1-3]. GLOBOCAN estimates that, globally, 432,000 deaths are caused by pancreatic cancer, and in 2018 there were 459,000 new cases [4]. Compared to other types of cancer, which have declining rates, pancreatic cancer is predicted to become the third leading cause of cancer death in 2025, surpassing breast cancer [5].

At an early stage, pancreatic cancer rarely shows any symptoms. If there are any symptoms at all, there are mostly non-specific. Common symptoms include weight loss, abdominal pain, steatorrhea and new-onset diabetes or worsening of pre-existing diabetes. In later stages, symptoms of jaundice, and light-colored stool, as well as other symptoms caused by the obstruction of the common biliary duct and/or pancreatic duct, will start to appear[6]. Notably, pancreatic cancer is frequently detected in autopsy studies due to its insidious nature [7, 8]. Around 63% of pancreatic cancers originate in the head of the pancreas, while those starting in the tail and body of the pancreas occur in around 12.8% and 9.8% of cases, respectively [3]. Tumors originating from the tail and body of the pancreas tends to be detected at more advanced stages, as they require more time to develop symptoms.

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Imaging studies also plays a role in detecting pancreatic cancer. They are used to assess tumor location and size, vascular involvement, regional involvement, and metastatic extent (e.g., liver, lungs, and peritoneum)[6]. Ultrasounds lacks specificity and sensitivity for the detection of small pancreatic cancer lesions due to the gas present in the gastrointestinal tract, making early diagnosis difficult [9]. A computed tomography (CT) scan with contrast remains the main modality to diagnose pancreatic cancer; for cancers smaller than 2cm, it has sensitivity up to 63 - 77% [10]. Magnetic resonance imaging (MRI) can be used if a CT scan is inconclusive, especially for iso attenuating pancreatic cancer [11]; however, CT scans and MRI do not warrant tumor detection, even when jaundice is already present. Therefore, an endoscopic ultrasound (EUS) examination can help in diagnosis [12].EUS has been reported to have a diagnostic rate of 45.5% for stage 0 and 81.8% for stage I cancers, compared to 9.7% and 63% for CT scans, as well as 9.7% and 39.1% for MRI, respectively [13, 14].

The prognostication of pancreatic cancer is mostly based on a tumor node metastasis (TNM) staging system[6]. The American Joint Committee on Cancer (AJCC) classifies TNM for pancreatic cancer into four stages: stage I a localized, resectable tumor, smaller than 2 cm (IA) and, larger than 2 cm but smaller than 4 cm (IB); stage II a larger tumor (>4cm) limited to the pancreas (IIA), and the involvement of 1-3 regional lymph nodes (LNs) with a tumor size <4 cm (IIB); stage III metastasis to ≥4 regional LNs, regardless of the tumor size; and stage IV distant metastasis [15]. The two most important prognostic factors are the size of the tumor upon detection (<2 cm) and early stage detection[16]. The United States National Cancer Institute data showed that only 12% of pancreatic cancer cases are detected at the local stage, with a 5-year survival rate of 44%; when the cancer is detected at stage III, which involves surrounding tissue, the 5-year survival rate drastically drop 15%; and for distant metastasis at which more than half of all patients are detected, the survival rate is only 3% [17]. Surgery, is still the most effective treatment in early-diagnosed pancreatic cancer; however only 10-20% are eligible for surgical resection upon detection[18, 19]. In patients diagnosed with metastatic tumors, the median survival time is only 3 months and 6-9 months for locally advanced stage cancer [20]. There is an urgent need to find diagnostic tools and methods that can detect pancreatic cancer at the earliest stage; our review will highlight novel biomarkers and the feasibility of using them.

2. Current Biomarkers

Currently, the only biomarker accepted by the FDA and National Comprehensive Cancer Network guidelines for pancreatic cancer is carbohydrate antigen 19-9 (CA19-9) [21, 22]. CA19-9 can be used as a prognostic factor, however it has little value for early diagnosis and screening [23, 24]. The ESMO clinical guidelines for pancreatic cancer stated that CA19-9 is not useful as a screening tool [6]. Previous studies have stated that CA19-9 has a mean sensitivity of 78.2% and a specificity of 82.8% for identifying pancreatic carcinoma [25]. Other types of tumors also show elevated CA19-9 levels, such as colorectal cancer, cholangiocarcinoma, liver cancer, and gastric cancer. Furthermore, in some benign conditions, such as obstructive jaundice and, cirrhosis, this tumor marker also shows elevated levels [14, 26]. Because CA19-9 is a sialylated Lewis antigen blood group people in the Lewis-antigen-negative blood group will not synthesize the specific antigen. It has been estimated that up to 10% of people do not express of Lewis antigens [27, 28]. Notably, a recent study by Liu et al. stated that Lewis-antigen-negative individuals experienced poorer outcomes when diagnosed with pancreatic cancer with higher metastatic rates [29].

The second most common biomarker used for pancreatic cancer is carcinoembryonic antigen (CEA). The sensitivity and specificity are reported to be 44.2% and 84.8% respectively [25]. Similar to CA19-9, CEA is mostly used as a prognostic marker for pancreatic cancer. It has been reported that in pancreatic cancer patients, 30-60% have elevated CEA levels [30]. CEA also appears in other types of cancers, including colon, breast, lung, and thyroid. When used as a single biomarker, CEA has a sensitivity of 43% and a specificity of 82%, which is even lower than CA19-9 [31].

CA19-9 and CEA can also be used as patient stratification tools during diagnosis. CA19-9 can be a predictor of lymph node metastasis, with a cut-off value of 400 U/mL [32]. A recent study by Esen

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et al. reported that CA 19-9 alone can be used to differentiate N0 from N2 patients, but not N1 [33]. However, it has been reported that using a CA19-9/CEA ratio can differentiate whether a patient is N0, N1, or N2. The sensitivity and specificity cut-off value of 27.8 has been reported at 79.4% and 80.4%, respectively [33]. The ability to differentiate N0 from N1 tumors will be a valuable tool, as N0 patients have greater probability of undergoing complete surgical resection.

3. Novel biomarker

3.1. Proteomic biomarkers

Novel protein biomarkers have been reported to be able to detect early-stage pancreatic cancer. Leucine-rich alpha-2 glycoprotein 1 (LRG1) is a glycoprotein that is part of the leucine-rich repeat (LRR) family of proteins. It is primarily involved in protein interactions, signal transduction, cell adhesion and development, and the promotion of new blood vessels. The overexpression of LRG1 has been correlated with poor survival and late tumor stage; furthermore, LRG1 promotes the viability, proliferation and invasion of pancreatic tumor cells [34-38]. Another biomarker tissue inhibitor is metalloproteinase 1 (TIMP-1), which is normally expressed to regulate of cell proliferation and apoptosis, with a sensitivity of 47.1%, a specificity of 69.2%, and AUC of 0.64 reported in diagnosing pancreatic cancer [39, 40]. Transthyretin (TTR) a thyroid hormone carrier (thyroxin and tri-iodothyronine), has been reported to be increased by more than 1.5-fold in the serum of pancreatic ductal adenocarcinoma (PDAC) patients compared to normal controls, with a sensitivity of 90.5, a specificity of 47.6, and AUC of 0.75 [41]. ICAM-1 is a glycoprotein involved in cell adhesion and a macrophage chemo attractant; several studies have evaluated the use of ICAM-1 as an early diagnostic tool for pancreatic cancer. By using a cut-off value of 878.5 u/mL, ICAM-1 exhibited a sensitivity, specificity, and AUC of 82%, 82.26%, and 0.851 respectively [42]. Another biomarker reported to have potential in the early detection of pancreatic cancer is osteoprotegerin (OPG), which has a role in bone homeostasis. Shi, et al. reported that OPG is upregulated in cancerous pancreatic tissue and the expression of which is even higher in patients with new-onset diabetes [43-45].

3.2. Combination of biomarkers

The use of multiple biomarkers or biomarker panels for early diagnosis has been proposed in several studies (Table 1). The use of a single tumor marker is reported to have a high probability of false positives and false negatives [46, 47]. Park, et al. were able to report a sensitivity of 82.5%, a specificity of 92.1%, and an AUC of 0.93 ($P < 0.01$) when using a proteomic multi-marker panel including LRG1, TTR, and CA19-9, which was 10% higher compared to CA19-9 alone [48]. In another study by using a panel of three biomarkers, CA 19-9, Intercellular Adhesion Molecule 1 (ICAM-1), and osteoprotegerin (OPG) researchers were able to discriminate healthy patients from patients with PDAC with a sensitivity of 88%, a specificity of 90%, and a AUC of 0.93 [49]. In a Korean study, Kim et al. were able to create a new biomarker combination consists of ApoA1, CA125, CA19-9, CEA, ApoA2, and TTR, with a sensitivity, specificity, and area under curve of 93%, 96%, and 0.993, respectively [50]. Interestingly, all six biomarkers that used are part of a pan-diagnostic kit that is commercially available in Korea to diagnose seven cancers, hepatocellular carcinoma, breast cancer, lung cancer, gastric cancer, colon cancer, prostate cancer, and ovarian cancer. In a case-control study, Mellby et al. were able to achieve a sensitivity and specificity of 94% and 95% in differentiating stages I and II from normal controls with an AUC of 0.96, by using biomarker signatures that consists of 29 biomarkers [51].

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Table 1. Biomarkers and combination biomarkers for the detection of pancreatic cancer.

Study reference	Biomarkers	Sensitivity	Specificity	AUC
Joergensen[40]	TIMP-1	47.1%	69.2%	0.64
Chen[41]	TTR	90.5%	47.6%	0.75
Mohamed[42]	ICAM-1	82%	82.6%	0.85
Park[48]	LRG1, TTR, CA19-9	82.5%	92.1%	0.93
Brand[49]	ICAM-1, OPG, CA19-9	88%	90%	0.93
Kim[50]	ApoA1, CA125, CA19-9, CEA, ApoA2, and TTR	93%	96%	0.993
Mellby[51]	Panel of 29 biomarker	94%	95%	0.96

3.3. miRNA

Micro-RNA (miRNA) is single-stranded RNA that was discovered in 1993, which consists of 19-25 nucleotides. These nucleotides are then transcribed into miRNA with 21-2 nucleotides [52, 53]. miRNAs belong to non-coding RNA, and although miRNAs are not translated into proteins, they still play a crucial role in the development and function of the normal human body, including cell division, differentiation, apoptosis, and angiogenesis. miRNAs can be identified according to their location cytoplasmic or nuclear and length, i.e., small (<200 base-pairs) or long (>200 base-pairs) [23, 54]. miRNA has been correlated with tumorigenesis and progression through apoptosis escape, epithelial mesenchymal transition (EMT), invasion, and poor clinical outcomes. The EMT is a process by which epithelial cells lose cell to cell adhesion and gain invasive properties similar to mesenchymal cells, which is important in the metastasis of pancreatic cancer [55, 56].

The expression of miRNAs is affected by the deletion, amplification, translocation and integration of DNA during carcinogenesis. As a consequence miRNAs may be detected or overexpressed in certain cancers and used as biomarkers [23]. miRNAs can be detected in blood serum, plasma, cells, and tissues using reverse transcription-quantitative PCR (RT-qPCR), in situ hybridization, next-generation sequencing, and miRNA micro arrays [21, 56, 57]. In a four-stage study conducted by Zhou, et al. using qRT-PCR assays, they were able to identify six-miRNA signatures, including miR-122-5p, miR-125b-5p, miR-192-5p, miR-193b-3p, miR-221-3p, and miR-27b-3p, that could discriminate pancreatic cancer patients from normal controls with an AUC of 0.977 (95% CI: 0.894–0.979; sensitivity = 88.7%; and specificity = 89.1%) [58]. They also reported that miR-125b-5p could be used as an independent biomarker in predicting the survival rates of pancreatic cancer patients.

Serum miR-25 has been reported to be overexpressed in patients with PDAC. High levels of miR-25, and miR 25-3p suppresses PH domain leucine-rich repeat protein phosphatase 2 (PHLPP2), which results in the malignant phenotype of pancreatic cells via the activation of oncogenic AKT-p70S6K signaling. The overexpression of miR-25-3p has been correlated with a worse prognosis in pancreatic cancer patients [59]. The overexpression of miR-25 has also been reported in gastric cancer, lung cancer, and cholangiocarcinoma; other studies have suggested that miR-25 serves as a tumor suppressor in thyroid cancer and colon cancer [60-64]. When miR-25 was combined with CA19-9 to differentiate pancreatic cancer patients from normal controls, an AUC-ROC of 0.985, a sensitivity of 97.5%, and a specificity of 90.11% were achieved; for the detection of stages I and II tumors, miR-25 and CA19-9 were able to detect 40 out of 42 patients (95.24%). These results suggest that miR-25 may be used as a new biomarker for the early detection of pancreatic cancer [65].

Schultz. et al, were able to identify two panels of miRNAs that are dysregulated in pancreatic cancer [66]. Panel 1 consisted of miR-145, miR-150, miR-223, and miR-636, and panel 2 consisted of miR-26b, miR-34a, miR-122, miR-126 miR-145, miR-150, miR-223, miR-505, miR-636, and miR-885.5p. These miRNA panels were able to distinguish pancreatic cancer patients from healthy subjects. Using

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panel 1, an AUC of 0.86 (95% CI: 0.82-0.90), a sensitivity of 0.85 (95% CI: 0.79-0.90), and a specificity of 0.64 (95% CI: 0.57-0.71) were achieved. Using panel 2 an AUC of 0.93 (95% CI: 0.90-0.96), a sensitivity of 0.85 (95% CI; 0.79-0.90), and a specificity of 0.85 (95% CI: 0.80-0.85) were achieved. Interestingly, when combined with CA19-9, both panels were able to detect stages IA-IIB pancreatic cancer with the following performance; panel 1 an AUC of 0.83 (95% CI: 0.76-0.90); panel 2 an AUC of 0.91 (95% CI: 0.86-0.95). In a similar study conducted by Johansen, et al. they used 4-panels, panel I (7 miRNAs), panel II (9 miRNAs), panel III (5 miRNAs), and panel IV (12 miRNAs). Patients with pancreatic cancer in panels I and II were compared to patients with chronic pancreatitis and healthy people combined; in contrast, patients with pancreatic cancer in panels III and IV were compared to healthy participants (Table 2). Panels I and III were designed to be robust to technical variation, and panels II and IV included all significant miRNAs from a multivariate model, thus it representing the upper limit in terms of training [67]. The best panel to discriminate stages I and II pancreatic cancer from healthy subjects was panel II combined with serum CA19-9, exhibiting a sensitivity of 0.77 (0.69-0.84), a specificity of 0.94 (0.90-0.96), and an AUC of 0.93 (0.90-0.96). It is noteworthy that the aforementioned studies did not share any miRNA in their panels, except for miR-25.

Table 2. Four diagnostic microRNA panels: panels I and II compare patients with pancreatic cancer to chronic pancreatitis patients and healthy persons; panels III and IV compare pancreatic cancer patients to healthy persons only [67].

Panel I	Panel II	Panel III	Panel IV
miR-16	miR-16	miR-16	miR-16
miR-27a	miR-24	miR-27a	miR-18.a
miR-30a.5p	miR-27.a	miR-25	miR-24
miR-323.3p	miR-30a.5p	miR-29c	miR-27a
miR-20a	miR323.3p	miR-483.5p	miR30a.5p
miR-29c	miR-20a		miR-323.3p
miR-483.5p	miR-25		miR-20a
	miR-29c		miR-25
	miR-483.5p		miR-29c
			miR-191
			miR-345
			miR-483.5p

Other than serum and pancreatic tissue samples, miRNAs can also be found in feces, urine, and saliva. miR-143, miR-223 and miR-30 can be found in urine and detected in stage I cancer. The combination of miR-143 and miR-30 showed a sensitivity and specificity of 83.3% and 96.2%, along with an AUC of 0.92 [68, 69]. The measurement of miR-1246 and miR-4644 in saliva has been studied to distinguish pancreatic cancer patients from healthy controls, with AUC values for the ROC curves of 0.814 (P = 0.008) and 0.763 (P = 0.026), respectively; when miR-1246 and miR-4644 were combined, the AUC increased to 0.833 (P = 0.005) [70]. Salivary miRNAs were reported to be stable due to the protection of exosomes. In the stool samples of pancreatic cancer patients, miR-21 and miR-155 were found to be overexpressed (P = 0.0049 and P = 0.0112, respectively), with a lower expression of miR-216 levels (P = 0.0002). The combination of miR-21, miR-155, and miR-216 for pancreatic cancer screening exhibits a sensitivity of 83.3%, a specificity of 83.3%, and an AUC of 0.866 (95% CI: 0.7722-0.9612) [71].

3.4. Circulating DNA

Circulating-free tumor DNA (ctDNA) was first described in 1948, and it has been postulated that DNA release via the necrosis, apoptosis, and lysis of circulating tumor cells (CTCs) and micro-metastasis contributes to the presence of ctDNA [72-74]. ctDNA consists of 170-181 base pairs and is found in body fluids at a very low concentrations ranging from 1 to 100 ng/mL, depending on the type and tumor burden [47, 75]. Due to its low concentration in body fluids, it requires high analytical

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sensitivity and specificity for detection. The methods used to detect ctDNA include real-time PCR, automatic sequencing, mass spectrometry genotyping, next-generation sequencing (NGS), and digital PCR platforms (such as digital droplet PCR, (ddPCR)) with the sensitivity of these methods greatly varies, ranging between 0.01% and 15% [76-79].

ctDNA has been reported to be higher in patients with pancreatic cancer. In particular, Shapiro, et al. detected ctDNA levels as low as 25 ng/mL and DNA levels above 100 ng/mL as the upper normal limit using radioimmunoassay DNA quantification [80]. The KRAS gene has received significant attention in terms of ctDNA mutations because it is highly mutated in pancreatic cancer [77]. Samples from 26 pancreatic cancer patients were assessed for 54 of their genes, and it was reported that KRAS, TP53, APC, FBXW7, and SMAD4 may be able to detect PDAC [81]. ctDNA KRAS mutation for the diagnosis of PDAC was reported to have a sensitivity of 47% and a specificity of 87%, and when combined with CA19-9, it had a sensitivity of 98% and specificity of 77% [82]. On the contrary, Cohen et al. reported that CA19-9 was superior to ctDNA for the detection of stages I and II PDAC [83]. Studies of ctDNA have reported mixed results. In a study of 26 cancer patients, it was found that KRAS, TP53, APC, FBXW7, and SMAD4 mutations were found in 90% of matched tumor biopsies utilizing NGS technology. The diagnostic accuracy was reported to be 97.7%, with an average sensitivity of 92.3%, and a specificity of 100% across all five investigated genes [84]. On the contrary, Pishavian et al. reported that overall concordance between blood and tissue samples was only 25%using NGs assays, and mutations in KRAS were only detected in 29% of blood samples in comparison to 87% in tumor tissue biopsies [85]. Similarly, in another study researchers evaluated the correspondence of KRAS mutations in pancreatic cancer tissue as well as ctDNA and KRAS mutations in serological markers, reporting that KRAS mutations were detected in 70% of neoplastic tissue samples, though none were found in ctDNA samples [86].

Currently, the use of ctDNA as a diagnostic tool is limited due to the low amount of detectable ctDNA in the early stage of disease [87]. However, ctDNA has been reported to be correlated with tumor burden and could be used as a tool to predict treatment response and surveillance in advanced cases [88]. Chen et al. reported that KRAS-mutant ctDNA was correlated with time to progression and overall survival, with detection rates of 93.7% and 86.4% in patients with non-elevated CA19-9. KRAS mutations were also correctly predict 80% of patient response to treatment [89]. Patients with KRAS-mutant ctDNA were reported to have 6.1 months of disease-free survival in comparison to 16.1 months in patients that had no such mutation, with overall survival times of 13.3 and 27.6 months, respectively ($p < 0.001$) [90]. Similarly, a recent study utilizing ddPCR reported that KRAS-mutated ctDNA was correlated with a poorer prognosis, at 170 days vs. 489 days; interestingly, the presence of KRAS mutation in tissue DNA was not associated with survival rates [91]. A subtype of a specific KRAS mutation, p.G12V,was also associated with shorter survival compared to p.G12D, p.G12R, or wild type variants [91]. Serial plasma testing of KRAS-mutant ctDNA in advanced PDAC patients receiving chemotherapy seems to allow better monitoring than CA 19.9 [92]. Longitudinal monitoring of ctDNA has been reported to predict response to therapy and disease progression around 5 months earlier than standard radiological imaging and CA19-9 9 [93, 94].

The use of ctDNA is still limited because of signature ctDNA concordance between tissue biopsy and liquid biopsy, which greatly varies from 48% to 100% [90]. Additionally, there is a lack of protocol standardization, the reliability of ctDNA detection methods varies between studies, and there are only a limited number of validation studies available [77]. Furthermore, since tumor entities other than pancreatic cancer also show mutations low diagnostic sensitivity and specificity have been observed [47]

3.5. Circulating Tumor Cells (CTC)

Circulating tumor cells, which are intact cells shed by tumors and circulate in the body can be detected in the blood [95]. After shedding, the circulating tumor cells can disseminate through blood vessels and invade local tissue stoma [96-98]. It has been reported that CTCs can be detected before metastasis [99]. CTCs were reported to be present in whole blood at a ratio of around 1 for every 107 leukocytes per mL, with a half-life estimated at around 1-2.4 hours [100]. The identification of CTCs

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includes the process of CD45 depletion to remove leukocytes; then, the enrichment of CTCs is performed via size-based filtration or epithelial cell adhesion molecules (EPCAMs). The actual CTC recognition involves examining cell morphology and measuring the expression of particular gene markers or proteins via the immunofluorescence of molecules specific for CTCs [47, 100]. Another CTC detection method utilizes genomic, transcriptomic and proteomic approaches; one of the most widely used is FDA-approved Cell Search® [100]. Methods for detecting CTCs are challenging, as there are only a low number of captured CTCs [101]. Furthermore, in the case of pancreatic cancer, it has been reported to have a lower detection rate in comparison to other tumors [77].

Several studies have reported that CTCs may have sufficient sensitivity to detect stage I and II cancer. Kulemann et al. detected CTCs in 80% of early-stage IIA and IIB tumors in 8 out of 10 patients using immunofluorescence for an epithelial-to-mesenchymal transition (EMT) marker and an epithelial antigen cytokeratin (CK); in contrast, CTCs were not found in any of the 10 control patients ($p < 0.001$) [102]. Similarly, Xu et al. using negative enrichment (NE), immunofluorescence, and in situ hybridization (FISH) of chromosome 8 (NE-iFISH), were able to detect CTCs in 90% of pancreatic cancer patients; when combined with CA19-9, the diagnostic rate was reported to reach 97.5%, 75% in benign disease, and 73% in early-stage pancreatic cancer [103]. Furthermore, Rhim et al. reported capturing CTCs in 33% of patients with cystic lesions without a clinical diagnosis of cancer (Sendai criteria), 73% with PDAC, and no detection in patients without cysts or cancer [104]. Although promising, the use of CTC as an early biomarker is not yet suitable for clinical settings and still requires studies involving higher number of samples.

4. Screening Feasibility

Developing pancreatic screening criteria is challenging, and population-based screening is not feasible. In the general population, with no risk stratification applied, the lifetime risk of developing pancreatic cancer up to the age of 70 years is approximately only 1.3% [20]. The screening of the general population is not cost-effective, and there is no evidence that it reduces mortality [105, 106]. Similarly, the US Preventive Service Task Force recommends against screening for asymptomatic patients [105, 107, 108].

Routine screening is recommended for individuals with inherited genetic abnormalities such as a familial history of pancreatic cancer and Peutz-Jeghers syndrome [109]. The age of first screening is still debated among investigators. Generally, however, it is reported that screening should be performed at the age of 40-50 years or 10-15 years earlier than the onset age of family members diagnosed with pancreatic cancer [110]. The International Cancer of the Pancreas Screening Consortium recommends surveillance should begin at 50 years old or 10 years earlier than the youngest blood relative with pancreatic cancer. Screening is performed every 3 years or every 3-6 months if there are abnormalities [110, 111].

The NCCN recommends EUS as a screening tool; in a study of 78 high-risk individuals CT and EUS were able to identify 8 patients with pancreatic cancer, 6 with intraductal papillary mucinous neoplasm (IPMN), and 3 patients with extra pancreatic neoplasm [21, 22, 112]. Canto et al. reported that EUS, MRI, and CT were able to detect pancreatic lesions in asymptomatic patients with detection rates reaching 42.6%, 33.3%, and 11.0%, respectively [109]. In the International Cancer of the Pancreas Screening Consortium, three fourth of experts agreed that EUS and MRI are the preferred methods of screening in comparison to CT, which is due to the higher detection rates; however, there was no consensus on how frequently screening should be performed [107].

Several unhealthy lifestyles and living habits have been linked to an increased risk of developing pancreatic cancer. Cigarette smoking has been reported to increase the risk of pancreatic cancer by 2-3-fold [113]. Heavy alcohol intake has been described as an independent risk factor that contributes to pancreatic cancer risk in men (hazard ratio (HR = 1.69, 95% CI: 1.21–2.37) [114, 115]. Another major risk factor is diabetes mellitus (DM). The association between DM and pancreatic cancer has been observed since the 1800s; however, the exact mechanism is still not fully understood [116, 117]. The prevalence of DM in patients with pancreatic cancer ranges from 4 to 65% [118-120]. Another study by Pannala et al. reported that 47% of pancreatic cancer cases were detected in patients with DM, in

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comparison to the control group in which only 7% had DM, and 74% of them had new- onset DM [121]. Glucose homeostasis disturbance is shown to be universal in pancreatic cancer patients, and PDAC is reported to be the most consistent diabetogenic cause in humans, consequently making it the most common phenotypic trait of pancreatic cancer [122]. Abnormalities in fasting blood glucose levels have been detected at 30-36 months before pancreatic cancer diagnosis were made. Glucose levels progressively increased up to 126 mg/dL at approximately 6-12 months before cancer diagnosis [123]. Another study also reported that the mean interval between the onset of diabetes and pancreatic cancer was 10 months and ranges from 5-29 months [124]. A clinical diagnostic model called Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC), which uses three parameters (age, changes in blood glucose, and changes in body weight), was able to identify patients who developed pancreatic cancer within 3 years of diabetes onset, with an AUC of 0.87, sensitivity of 80%, and specificity of 80% [125]. Another clinical model was established through the Peking Union Medical College Hospital (PUMCH) which includes 10 risk factors (gender, age, alcoholic intake, smoking, diabetes mellitus history, high meat consumption, a family history of pancreatic cancer, chronic pancreatitis, cholelithiasis history, and cholecystitis history) reaching a sensitivity of 88.9%, a specificity of 97.6%, and an AUC of 0.98 [126].

5. Conclusion

As a tumor with a poor prognosis, particularly because most of pancreatic cancer cases are detected at advanced stages, there is an urgent need for early diagnostic tools. Besides early diagnostic tools, a more accurate and targeted screening and prediction model is yet to be established for pancreatic cancer.

Ideally, biomarkers should distinguish healthy subjects from patients, and be detected early, easy to measure, and cost-effective, with reproducible results. Recently, the novel biomarkers being investigated have shown promising results. However, they still require further validation studies as sample sizes have been limited. Furthermore, the methods used to measure novel biomarkers still vary between studies, consequently leading to highly non-reproducible results. Cost-effectiveness in measuring new biomarkers should also be considered, as well as the time required to validate novel biomarkers until they can be applied in clinical practice. The authors agree that studies should be more focused on early detection methods and models that are realistic, more applicable in clinical settings, practical, and ready for widespread use. We have read, with great interest, about a pan-diagnostic cancer tool available in Korea. It uses several well-known biomarkers and has been reported to predict multiple cancers at a cost of USD 300 [50]. Improving clinical diagnostic models will greatly help in identifying individuals who are at a high-risk of developing pancreatic cancer; therefore, it is recommended that the screening of high-risk individuals be performed at an earlier stage.

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