Early-Onset Pancreatic Cancer: A Comprehensive Review of Epidemiology, Etiologic Factors, and Clinical Implications

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Abstract

Abstract

Background: Pancreatic cancer remains one of the most lethal malignancies worldwide, largely due to its aggressive biology, absence of effective population-based screening strategies, and frequent diagnosis at advanced stages. Although pancreatic ductal adenocarcinoma (PDAC) predominantly affects older individuals, an increasing body of evidence has identified a distinct subgroup of patients diagnosed at a younger age, commonly referred to as early-onset pancreatic cancer (EOPC), typically defined as pancreatic cancer occurring before 50 years of age. Despite representing a minority of pancreatic cancer cases, EOPC has attracted growing clinical interest because of its potentially unique epidemiologic characteristics, differential exposure to risk factors, higher prevalence of hereditary susceptibility, and implications for precision medicine and targeted prevention strategies.

Aim: This review aims to comprehensively summarize current evidence regarding the epidemiology, etiologic factors, and clinical implications of EOPC. Particular emphasis is placed on hereditary predisposition, environmental and lifestyle-related exposures, metabolic and inflammatory conditions, infectious contributors, and the distinctive clinical features that may influence diagnostic pathways and therapeutic decision-making in younger patients.

Methods: A narrative review of the literature was conducted using evidence derived from population-based studies, international consortium analyses, systematic reviews, meta-analyses, clinical guidelines, and landmark translational investigations addressing EOPC. Relevant data regarding epidemiologic trends, non-modifiable and modifiable risk factors, clinical presentation, diagnostic challenges, prognostic determinants, and emerging management considerations were synthesized.

Results: EOPC accounts for approximately 4–17% of pancreatic cancer diagnoses, although higher frequencies have been reported in certain regional cohorts. Compared with average-onset pancreatic cancer, EOPC demonstrates a stronger association with familial clustering and germline mutations involving genes such as *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A*. Modifiable factors including cigarette smoking, obesity, diabetes mellitus, pancreatitis, alcohol consumption, and possibly viral hepatitis may further contribute to disease development in susceptible individuals. Younger age at presentation may reduce clinical suspicion, potentially resulting in delayed diagnosis and more advanced disease at presentation. However, younger patients often exhibit better functional status and may be more likely to receive multimodality treatment approaches.

Conclusions: EOPC should be recognized as a clinically important subset of pancreatic cancer with distinct epidemiologic and etiologic characteristics. Improved understanding of its underlying risk profile may facilitate earlier recognition, optimize genetic counseling and surveillance strategies, and support the development of individualized preventive and therapeutic approaches. Future research should focus on refining risk stratification models and establishing evidence-based screening paradigms for high-risk younger populations.

Keywords: *Early-Onset, Pancreatic Cancer, Clinical Implications*

Introduction

Pancreatic cancer remains one of the most lethal malignancies worldwide and is characterized by aggressive tumor biology, late clinical presentation, and limited opportunities for curative treatment. Pancreatic ductal adenocarcinoma (PDAC), the predominant histologic subtype, accounts for approximately 90% of pancreatic cancers and is associated with a particularly poor prognosis. Despite advances in surgical techniques, systemic therapies, and supportive care, survival outcomes remain disappointing, largely because most patients present with unresectable or metastatic disease at diagnosis. Globally, pancreatic cancer is the seventh leading cause of cancer-related mortality and is projected to become an even greater contributor to cancer deaths in the coming decades, underscoring the need for improved prevention and early detection strategies.[1–3]

Although pancreatic cancer has traditionally been considered a disease of older adults, increasing attention has focused on patients diagnosed at a younger age. Early-onset pancreatic cancer (EOPC) is generally defined as pancreatic cancer occurring before the age of 50 years and represents approximately 4–17% of all pancreatic cancer cases. Despite its relatively low frequency, EOPC has emerged as a clinically significant subgroup because accumulating evidence suggests that younger patients may differ from their older counterparts with respect to risk factor profiles, genetic susceptibility, disease presentation, and therapeutic implications.[4,5]

Hereditary predisposition appears to play a particularly important role in EOPC, with younger patients demonstrating a higher prevalence of germline pathogenic variants involving genes such as *BRCA1*, *BRCA2, PALB2*, and *CDKN2A*. In addition, environmental and metabolic factors—including cigarette smoking, obesity, diabetes mellitus, alcohol consumption, and pancreatitis—have been implicated in pancreatic carcinogenesis and may contribute to earlier disease onset in genetically susceptible individuals. Emerging evidence has also highlighted the potential role of infectious and microbiome-related factors in pancreatic cancer development, although their contribution to EOPC requires further investigation.[6–8]

Recognition of EOPC has important clinical implications. Younger patients frequently present with symptoms similar to those observed in older adults; however, lower clinical suspicion in this age group may contribute to delays in diagnosis and advanced-stage disease at presentation. Conversely, younger individuals often have better performance status and may therefore tolerate aggressive multimodal treatment approaches more effectively. Furthermore, identifying hereditary susceptibility in EOPC has direct implications for genetic counseling, cascade testing, surveillance of high-risk relatives, and the implementation of personalized therapeutic strategies.[5,6]

Despite growing interest in this field, EOPC remains relatively underrepresented in pancreatic cancer research, and many aspects of its epidemiology and etiologic determinants are incompletely understood. Therefore, this review aims to comprehensively summarize the current evidence regarding the epidemiology, etiologic factors, and clinical implications of EOPC, with the goal of improving disease recognition and informing future preventive, diagnostic, and therapeutic approaches.

Epidemiology of Early-Onset Pancreatic Cancer

Pancreatic cancer is among the most lethal malignancies worldwide, with both incidence and mortality continuing to rise in many regions. According to GLOBOCAN 2020 estimates, approximately 495,000 new pancreatic cancer cases and 466,000 related deaths occurred globally, reflecting the aggressive nature of this disease and its close alignment between incidence and mortality rates. Although pancreatic cancer remains less common than several other gastrointestinal malignancies, its poor prognosis has contributed substantially to the global cancer burden. Demographic changes, increasing prevalence of metabolic risk factors, and improved diagnostic capabilities are expected to further increase the number of affected individuals in the coming decades.[9]

Traditionally, pancreatic cancer has been considered a disease of older adults, with the highest incidence observed between 60 and 80 years of age. However, a subset of patients develops pancreatic cancer considerably earlier in life. Early-onset pancreatic cancer (EOPC) is most commonly defined as

pancreatic cancer diagnosed before the age of 50 years, although slight variations in age cutoffs have been reported in the literature. The lack of a universally accepted definition has contributed to some heterogeneity in epidemiologic studies and may partially explain differences in reported frequencies across cohorts.[10]

Available evidence suggests that EOPC accounts for approximately 4–17% of all pancreatic cancer cases worldwide. Population-based analyses from Europe and North America consistently indicate that EOPC represents a minority of diagnoses, yet its recognition is clinically important because younger patients may exhibit distinctive etiologic and clinical characteristics. In a population-based study using data from the Surveillance, Epidemiology, and End Results (SEER) registry, Ansari and colleagues reported that EOPC constituted a relatively small but well-defined subgroup with demographic and survival patterns differing from those of older patients.[11] Similar findings have been reported in other retrospective and registry-based studies, supporting the concept that EOPC represents a unique clinical entity rather than merely an age-defined extension of conventional pancreatic cancer.[10,12]

Geographic variation in the frequency of EOPC has also been observed. While most international studies report frequencies below 15%, higher proportions have been described in selected populations. Notably, recent Egyptian data demonstrated that approximately one-fifth to one-quarter of pancreatic cancer patients were diagnosed before the age of 50 years, substantially exceeding rates reported in many Western cohorts. Although the reasons underlying these differences remain uncertain, they may reflect variations in genetic background, environmental exposures, healthcare access, referral patterns, or population age structures.[13]

Recent investigations have further emphasized the need to distinguish EOPC from average-onset pancreatic cancer in epidemiologic research. Younger patients appear more likely to harbor hereditary cancer syndromes and may have experienced prolonged exposure to modifiable risk factors beginning earlier in life. Improved characterization of EOPC epidemiology is therefore essential to inform targeted prevention strategies, optimize genetic testing recommendations, and identify individuals who may benefit from enhanced surveillance approaches.[10,14]

Etiologic Factors in Early-Onset Pancreatic Cancer

Non-Modifiable Risk Factors

Hereditary Predisposition and Germline Susceptibility

Inherited genetic susceptibility appears to play a more prominent role in early-onset pancreatic cancer (EOPC) than in pancreatic cancer diagnosed later in life. Familial pancreatic cancer, generally defined as the occurrence of pancreatic cancer in at least two first-degree relatives without an identifiable hereditary syndrome, accounts for approximately 5–10% of pancreatic cancer cases. Younger patients are more likely to harbor pathogenic germline variants, supporting the hypothesis that genetic predisposition contributes substantially to earlier disease onset. Recognition of these inherited susceptibilities is clinically important because it facilitates genetic counseling, cascade testing of family members, and implementation of surveillance strategies for high-risk individuals.[15,16]

Several germline mutations have been consistently associated with an increased risk of pancreatic cancer. Among these, *BRCA1* and *BRCA2* mutations are particularly relevant, given their established role in homologous recombination repair deficiency and their therapeutic implications. Additional susceptibility genes include *PALB2*, *CDKN2A*, *STK11*, and mismatch repair genes associated with Lynch syndrome. Emerging evidence suggests that these alterations may be identified more frequently among patients with EOPC than among those with average-onset disease, highlighting the importance of universal consideration of germline testing in younger patients diagnosed with pancreatic cancer.[16,17]

Sex and Host-Related Factors

Pancreatic cancer is generally more common in men than in women, a pattern that has also been observed in EOPC cohorts. Although this difference is likely influenced by variations in exposure to environmental risk factors such as smoking and alcohol consumption, biological factors may also contribute. Hormonal influences and sex-specific differences in metabolism and immune regulation

have been proposed; however, current evidence remains insufficient to establish a direct causal relationship between sex hormones and pancreatic carcinogenesis in younger populations.[18]

ABO Blood Group

ABO blood group status has emerged as a reproducible host susceptibility factor in pancreatic cancer. Individuals with non-O blood groups have consistently demonstrated a higher risk of developing pancreatic cancer compared with those with blood group O. Although the underlying mechanisms remain incompletely understood, hypotheses include altered inflammatory responses, variations in cell adhesion molecules, and interactions affecting host–microbial relationships. Despite this association, ABO blood type alone lacks sufficient predictive value for clinical screening purposes and should be interpreted within the broader context of individual risk assessment.[19]

Microbiota and Pancreatic Carcinogenesis

Growing evidence suggests that the microbiome may influence pancreatic carcinogenesis through complex interactions involving inflammation, immune modulation, and metabolic regulation. Prospective studies have demonstrated associations between specific oral microbial profiles and subsequent pancreatic cancer risk. Additionally, alterations in gut microbial composition have been implicated in obesity, insulin resistance, and chronic low-grade inflammation, all of which represent established contributors to pancreatic tumor development. While the precise role of microbiota in EOPC remains uncertain, these findings support the concept that host–microbe interactions may contribute to pancreatic cancer susceptibility and warrant further investigation in younger populations.[20,21]

Modifiable Risk Factors

Cigarette Smoking

Cigarette smoking is the most consistently established modifiable risk factor for pancreatic cancer and appears to play a significant role in early-onset pancreatic cancer (EOPC). Tobacco smoke contains numerous carcinogens, including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons, which can induce DNA damage and promote pancreatic carcinogenesis. Epidemiological studies have demonstrated a dose-dependent relationship between smoking exposure and pancreatic cancer risk, with current smokers exhibiting a substantially higher risk than never-smokers. Importantly, smoking cessation is associated with a gradual decline in risk over time, although excess risk may persist for several years after quitting. Given that smoking initiation often occurs during adolescence or early adulthood, prolonged cumulative exposure may contribute to earlier disease development in susceptible individuals.[22,23]

Obesity and Metabolic Dysfunction

Obesity has emerged as an important risk factor for pancreatic cancer and may be particularly relevant to EOPC. Excess adiposity contributes to insulin resistance, hyperinsulinemia, chronic low-grade inflammation, and alterations in adipokine secretion, thereby creating a pro-tumorigenic environment. Experimental studies further suggest that obesity-related metabolic disturbances may cooperate with oncogenic KRAS signaling to accelerate pancreatic neoplastic progression. Epidemiologic evidence indicates that elevated body mass index during early adulthood is associated with younger age at pancreatic cancer diagnosis, supporting the hypothesis that prolonged exposure to adverse metabolic conditions may influence the timing of disease onset.[24,25]

Alcohol Consumption

The relationship between alcohol intake and pancreatic cancer appears to be dose-dependent. While light-to-moderate alcohol consumption has not been consistently associated with increased risk, heavy alcohol intake has been linked to a modest but significant elevation in pancreatic cancer risk. Alcohol may contribute indirectly through recurrent pancreatic injury, promotion of chronic pancreatitis, oxidative stress, and enhancement of inflammatory pathways involved in carcinogenesis. Some studies have suggested that excessive alcohol consumption may be particularly relevant in EOPC, although its effect is likely modified by concomitant smoking and other environmental exposures.[16,26]

Pancreatitis

Both acute and chronic pancreatitis have been associated with an increased risk of pancreatic cancer. In

some patients, particularly those presenting with unexplained acute pancreatitis, pancreatic inflammation may represent an early manifestation of occult malignancy rather than a causal factor. Chronic pancreatitis, however, is recognized as a genuine predisposing condition, with repeated cycles of inflammation and tissue repair promoting genomic instability and malignant transformation. The association appears strongest among individuals with hereditary pancreatitis, persistent tobacco or alcohol exposure, and prolonged disease duration. Distinguishing chronic pancreatitis from pancreatic cancer remains a major clinical challenge because both conditions frequently share overlapping symptoms and imaging findings.[27–29]

Diabetes Mellitus

Diabetes mellitus demonstrates a complex bidirectional relationship with pancreatic cancer. Longstanding type 2 diabetes is associated with an approximately 1.5- to 2-fold increase in pancreatic cancer risk and may contribute to carcinogenesis through hyperinsulinemia, chronic inflammation, and metabolic dysregulation. Conversely, new-onset diabetes in adults may represent an early manifestation of occult pancreatic cancer, with the highest risk observed during the first few years following diabetes diagnosis. Recognition of this temporal relationship is particularly important in younger individuals because unexplained diabetes may occasionally provide an opportunity for earlier cancer detection.[30,31]

Viral Hepatitis

Although hepatitis B virus (HBV) and hepatitis C virus (HCV) are primarily recognized for their association with hepatocellular carcinoma, increasing evidence suggests that they may also contribute to pancreatic carcinogenesis. Meta-analyses have demonstrated a modest increase in pancreatic cancer risk among individuals with chronic HBV infection, while studies investigating HCV have produced somewhat less consistent findings. Proposed mechanisms include chronic systemic inflammation, immune dysregulation, oxidative stress, and direct viral effects on pancreatic tissue. However, the magnitude of these associations remains uncertain, and further studies specifically addressing their contribution to EOPC are warranted.[32,33]

Clinical Characteristics and Diagnostic Challenges of Early-Onset Pancreatic Cancer

The clinical presentation of early-onset pancreatic cancer (EOPC) largely resembles that of pancreatic cancer diagnosed later in life. Common symptoms include abdominal pain, unexplained weight loss, anorexia, nausea, and obstructive jaundice in patients with tumors involving the pancreatic head. However, because these manifestations are often nonspecific, diagnosis is frequently delayed until the disease has progressed to an advanced stage. Younger adults are generally perceived as being at lower risk for pancreatic malignancy, which may reduce the initial index of clinical suspicion and contribute to prolonged diagnostic intervals.[34,35]

Several studies comparing EOPC with average-onset pancreatic cancer have demonstrated that younger patients often experience a delay between symptom onset and definitive diagnosis. Early symptoms may be attributed to more common benign gastrointestinal conditions, including dyspepsia, peptic ulcer disease, functional bowel disorders, or biliary pathology. Consequently, repeated healthcare encounters may occur before pancreatic imaging is pursued. This diagnostic delay has important implications because pancreatic cancer progression is often rapid, and even relatively short postponements in diagnosis may adversely affect resectability and survival outcomes.[35,36]

The stage at presentation in EOPC remains an area of ongoing investigation. While some cohorts have reported a higher prevalence of locally advanced or metastatic disease among younger patients, others have found comparable stage distributions between early- and average-onset groups. These discrepancies likely reflect differences in study design, healthcare access, referral pathways, and population characteristics. Nevertheless, the potential for delayed recognition in younger individuals underscores the importance of maintaining clinical vigilance when evaluating persistent alarm symptoms, particularly in patients with additional risk factors such as smoking history, familial predisposition, pancreatitis, or new-onset diabetes.[35,37]

Despite concerns regarding delayed diagnosis, younger patients frequently exhibit better performance

status and lower comorbidity burden than older individuals at the time of diagnosis. These characteristics may increase eligibility for aggressive multimodal treatment strategies, including intensive chemotherapy regimens, surgical resection, and participation in clinical trials. Consequently, age alone should not be considered a barrier to comprehensive oncologic assessment and management in patients with EOPC.[38]

From a diagnostic perspective, no EOPC-specific biomarkers currently exist. Serum carbohydrate antigen 19-9 (CA19-9) remains the most widely used biomarker in pancreatic cancer; however, its utility in early detection is limited by suboptimal sensitivity and specificity, particularly in small-volume disease. In addition, CA19-9 may be elevated in several benign pancreaticobiliary conditions and is not expressed in Lewis antigen-negative individuals. Therefore, CA19-9 should be interpreted cautiously and primarily as an adjunct to imaging and histopathologic evaluation rather than a stand-alone diagnostic tool.[39]

Cross-sectional imaging remains central to the diagnosis of pancreatic cancer. Pancreatic-protocol computed tomography (CT) is generally considered the initial imaging modality of choice because it enables simultaneous evaluation of the primary tumor, vascular involvement, and distant metastatic disease. Endoscopic ultrasound (EUS) provides additional diagnostic value, particularly for small lesions or cases with indeterminate CT findings, while also facilitating tissue acquisition through fine-needle aspiration or biopsy. Given the increased prevalence of hereditary susceptibility among younger patients, timely diagnostic evaluation and consideration of germline testing are essential components of EOPC management.[40,41]

Prognostic Features and Clinical Implications of Early-Onset Pancreatic Cancer

Survival outcomes in early-onset pancreatic cancer (EOPC) remain heterogeneous across published studies. While some investigations have demonstrated improved survival among younger patients compared with those diagnosed at older ages, others have reported comparable or even less favorable outcomes after adjustment for disease stage and treatment variables. These inconsistencies likely reflect differences in study populations, healthcare systems, treatment accessibility, and the biological heterogeneity of pancreatic cancer itself. Importantly, age at diagnosis should not be viewed as an isolated prognostic determinant; rather, outcomes appear to result from the complex interplay between tumor biology, disease stage, treatment intensity, and patient-related factors.[42,43]

One of the most consistent observations in EOPC cohorts is the greater likelihood of receiving aggressive multimodal therapy. Younger patients often have fewer comorbid conditions and better functional status, increasing their eligibility for surgical resection, combination chemotherapy regimens, and enrollment in clinical trials. This higher treatment intensity may partially explain the survival advantage reported in some studies. Conversely, when advanced disease is present at diagnosis, the aggressive biological behavior of pancreatic cancer may negate the potential benefits conferred by younger age.[44,45]

Increasing evidence also suggests that EOPC may exhibit distinctive molecular characteristics with important prognostic and therapeutic implications. Studies evaluating genomic profiles have identified a relatively higher prevalence of germline alterations affecting DNA damage repair pathways, including mutations involving *BRCA1*, *BRCA2*, and related susceptibility genes. Identification of these alterations is clinically relevant because they may predict enhanced responsiveness to platinum-based chemotherapy and eligibility for maintenance treatment with poly (ADP-ribose) polymerase (PARP) inhibitors. Therefore, comprehensive germline testing should be strongly considered in patients diagnosed with EOPC, regardless of family history.[46,47]

The recognition of hereditary predisposition extends beyond individual patient management and has important implications for family members. Cascade genetic testing may facilitate identification of unaffected relatives who carry pathogenic variants and who may benefit from surveillance programs designed for high-risk individuals. Although universal screening for pancreatic cancer is not currently recommended in the general population, targeted surveillance among genetically susceptible individuals offers an opportunity for earlier detection of precursor lesions or localized disease. Consequently, EOPC

serves as a clinical context in which oncology, gastroenterology, and genetic medicine intersect to enable more personalized preventive strategies.[46]

Recent advances in precision oncology have further expanded the therapeutic landscape of pancreatic cancer. Molecular characterization increasingly informs treatment decisions through the identification of actionable alterations and enrollment in biomarker-driven clinical trials. While only a minority of patients currently derive benefit from targeted approaches, the relatively greater prevalence of hereditary susceptibility in EOPC suggests that younger patients may be particularly well positioned to benefit from ongoing developments in individualized cancer therapy. Continued integration of molecular diagnostics into routine clinical practice is therefore likely to influence future management paradigms for EOPC.[47,48]

Despite these advances, the overall prognosis of pancreatic cancer remains poor, highlighting the importance of earlier recognition and effective risk stratification. Enhanced awareness of EOPC among clinicians, timely evaluation of suggestive clinical presentations, and appropriate utilization of genetic counseling services may improve opportunities for intervention. Future research should aim to clarify the biological distinctions underlying EOPC and determine whether age-specific approaches to surveillance and management can meaningfully improve patient outcomes.[42,49]

Conclusions

Advances in genomic profiling, liquid biopsy technologies, artificial intelligence-based risk prediction models, and multi-omics approaches offer promising opportunities to improve the early identification of individuals at increased risk for early-onset pancreatic cancer (EOPC). Given the relatively greater contribution of hereditary susceptibility and potentially prolonged exposure to modifiable risk factors in younger patients, future research should focus on refining risk stratification strategies and evaluating targeted surveillance programs for high-risk populations. Large prospective studies are also needed to clarify the biological distinctions between EOPC and average-onset pancreatic cancer and to determine whether age-specific preventive and therapeutic approaches can improve clinical outcomes. In conclusion, EOPC represents a clinically important subset of pancreatic cancer characterized by unique epidemiologic patterns, a stronger association with inherited predisposition, and distinct diagnostic and management challenges. Increased awareness of its etiologic factors and clinical implications may facilitate earlier recognition, optimize genetic counseling and individualized care, and ultimately contribute to improved outcomes through more personalized prevention and treatment strategies.

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