Protocol

Implementation of a Prefecture-Wide Regional Referral System for Early Detection of Pancreatic Cancer in Hiroshima, Japan: Protocol for a Multicenter Prospective Observational Study (Hi-PEACE Project)

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, and early detection is essential to improve clinical outcomes. However, many patients with early-stage PDAC are asymptomatic, complicating detection in routine clinical practice. Population-based screening for PDAC is not currently recommended given its low incidence and

cost-effectiveness concerns. Therefore, regional collaboration between primary care physicians and specialist centers may facilitate identifying individuals with PDAC risk factors or suspicious pancreatic imaging findings warranting further evaluation.

Objective: This study aims to describe the protocol for a prefecture-wide regional collaboration program in Hiroshima Prefecture, Japan, and evaluate its operation and diagnostic yield, particularly for the detection of stage 0 or I PDAC.

Methods: The Hiroshima Pancreas Cancer Early Diagnosis With Collaboration and Examination (Hi-PEACE) project is a multicenter prospective observational study conducted in Hiroshima Prefecture. The project involves 20 core hospitals covering all 7 secondary medical care areas. Eligible participants are adults aged 20 years or older with PDAC risk factors or suspicious pancreatic imaging findings. Risk factor–based referral criteria include low- and high-grade risk factors based on relative risks in the Japanese Clinical Practice Guidelines for PDAC, previous studies on early-stage PDAC, and feasibility in primary care settings. Participants are identified through 2 pathways: risk factor assessment and imaging abnormalities, including indirect pancreatic findings such as main pancreatic duct dilatation, pancreatic duct stenosis, and pancreatic cysts. Individuals meeting referral criteria are referred to core hospitals for detailed pancreatic evaluation, with computed tomography, magnetic resonance imaging, endoscopic ultrasonography, and, when clinically indicated, pathological diagnosis. The primary outcome is the number and proportion of participants diagnosed with early-stage PDAC, defined as stage 0 or I disease, among participants referred through the Hi-PEACE project. Secondary outcomes include the number and proportion of participants diagnosed with PDAC and those who undergo surgical resection, distribution of PDAC risk factors and suspicious pancreatic imaging findings, diagnostic procedures performed at core hospitals, treatment status, and prognosis. The operation of the regional referral system will also be evaluated descriptively using annual referral volumes and the distribution of referrals across participating hospitals and secondary medical care areas.

Results: Participant enrollment began on November 20, 2022. As of December 31, 2025, a total of 9,866 participants had been enrolled, and enrollment is planned to continue until December 31, 2028. Data collection and analysis are ongoing. The overall study period is planned to last until December 31, 2030.

Conclusions: The Hi-PEACE project is a prefecture-wide collaborative program designed to promote early detection of PDAC through structured referrals to specialist centers. This study will provide information on referral activity and diagnostic yield, particularly for stage 0 and I PDAC, and may inform the development of similar regional early detection programs. Further comparative studies and long-term follow-up will be needed to evaluate the impact of such programs on clinical outcomes.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a poor prognosis (5-year survival rate of approximately 10%) [1]. Conversely, the 5-year survival rate is 85.8% in patients with Union for International Cancer Control stage 0 disease (carcinoma in situ) and 68.4% in those with stage IA disease, defined as a tumor measuring 20 mm or less confined to the pancreas without lymph node metastasis [1,2]. Nevertheless, according to the cancer registry, Union for International Cancer Control stages 0 and IA account for only 1.7% and 4.1% of all patients with PDAC, respectively [2]. Collectively, these findings indicate that early diagnosis is essential for improving the prognosis of patients with PDAC but remains challenging in clinical practice.

One reason why early diagnosis of PDAC is difficult is that many patients with early-stage disease are asymptomatic [3,4]. In addition, population-based screening for PDAC is not currently recommended because of its low prevalence in the general population and concerns regarding cost-effectiveness [5]. Therefore, approaches to earlier diagnosis may need to focus less on mass screening of the general population and more on identifying individuals who may be at increased risk in routine clinical practice.

Recent reports from the Japanese Study Group on the Early Detection of Pancreatic Cancer and Hiroshima University, together with their affiliated hospitals, have described surgically resected cases of early-stage PDAC [3,4]. These studies showed that approximately 70% to 75% of patients with stage 0 or stage I PDAC exhibited no symptoms and were identified through abnormalities detected at health checkups, during surveillance, or in tests for unrelated conditions. Additionally, approximately 70% of these patients had known risk factors for PDAC [4], suggesting that attention to such factors may help identify individuals who warrant further evaluation. Abnormal pancreatic imaging findings detected during health checkups or routine follow-up may also provide important clues for early diagnosis of PDAC [4]. Specifically, both pancreatic mass lesions and indirect findings such as main pancreatic duct dilatation, pancreatic duct stenosis, and pancreatic cysts may prompt further diagnostic assessment and referral to specialist centers. Collectively, these findings suggest that identifying asymptomatic individuals with clinical risk factors or

suspicious pancreatic imaging findings may be important for early PDAC detection in routine clinical practice.

In Japan, several regional programs based on collaboration between community physicians and designated referral hospitals have reported an increase in patients diagnosed with early-stage PDAC. In particular, the Onomichi model suggests that ultrasonographic screening of individuals with PDAC risk factors, along with referral of patients with indirect pancreatic findings to specialist centers, may help detect resectable PDAC [6]. Similar programs have been introduced in other municipalities across Japan [7]. Hiroshima Prefecture has a health care structure with pancreatic specialists available across all secondary medical care areas, which are regional health care zones used for health care planning in Japan. This structure may make it feasible to develop a prefecture-wide, standardized referral program rather than a city-based initiative.

In Hiroshima Prefecture, the program has been implemented as a prefecture-wide initiative in cooperation with local medical associations, administrative bodies, and specialist centers. This initiative was named the Hi-PEACE (Hiroshima Pancreas Cancer Early Diagnosis With Collaboration and Examination) project. To our knowledge, the Hi-PEACE project is the first prefecture-wide collaborative program in Japan designed to promote the early detection of PDAC through standardized referral from primary care physicians to core hospitals with pancreatic specialists. Unlike conventional screening approaches focused primarily on detecting pancreatic mass lesions, the Hi-PEACE project emphasizes indirect pancreatic imaging findings and structured referral pathways integrated into routine primary care practice. The Hi-PEACE project was designed as a regional collaboration program integrated into routine clinical practice rather than a population-based screening program. The primary objective of the present prospective observational study is to evaluate the diagnostic yield of this program, particularly the number and proportion of referred participants diagnosed with stage 0 or I PDAC. Secondary objectives include describing referral activity across the 7 secondary medical care areas, diagnostic procedures performed at core hospitals, and the clinical characteristics and outcomes of patients diagnosed with PDAC. These evaluations are intended to characterize the operation and diagnostic outcomes of the regional collaboration program rather than establish its causal effectiveness.

Methods

Study Design and Setting

This is a multicenter prospective observational study. Hiroshima University serves as the coordinating center and principal institution and is responsible for data collection and analysis. Participating institutions include Hiroshima University Hospital and collaborating institutions in Hiroshima Prefecture. The study period extends from the date of approval to December 31, 2030, and the participant enrollment period is from November 20, 2022, to December 31, 2028.

This study is conducted in collaboration with the Hiroshima Prefecture Medical Association. Hiroshima Prefecture is divided into 7 secondary medical care areas, which are regional health care zones used for health care planning in Japan. Within each area, primary care physicians collaborate with designated referral hospitals where pancreatic specialists are available, hereafter referred to as core hospitals. The project involves 20 core hospitals covering all 7 secondary medical care areas in Hiroshima Prefecture. This regional network is designed to facilitate the identification and referral of individuals at increased risk of PDAC.

Participants

Eligible participants are adults aged 20 years or older who attend Hiroshima University Hospital, collaborating institutions, or primary care clinics affiliated with participating district medical associations and who have PDAC risk factors or suspicious pancreatic imaging findings. Participants are excluded if they are diagnosed with PDAC before referral through the Hi-PEACE project or if they decline to have their clinical data used for this study through the opt-out process. To avoid duplicate registrations, each participant is assigned a unique study identification number, and duplicate referrals for the same participant are counted only once. Patients already undergoing diagnostic evaluation or treatment for confirmed PDAC at another institution before referral are not included as newly identified participants through this project.

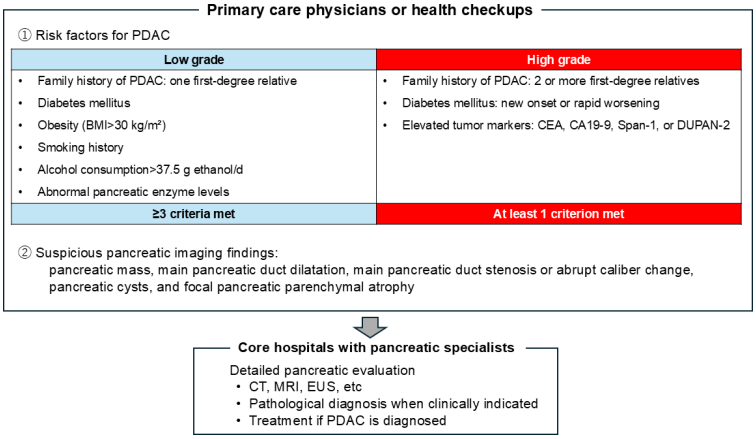
Identification and Referral Criteria

Identification criteria were established based on the relative risks described in the Japanese Clinical Practice Guidelines for PDAC and findings from previous studies [3,4,8,9]. Patients are identified through 2 pathways: risk factor assessment and imaging abnormalities.

Risk Factor–Based Identification

Risk factor–based referral criteria were developed as practical operational guidelines for routine clinical practice. Therefore, the classification of risk factors as low grade or high grade is based not only on the relative risks reported in the Japanese Clinical Practice Guidelines for PDAC but also on clinical feasibility, ease of recognition by primary care physicians, and the need to avoid excessive referrals while maintaining sensitivity for possible early-stage PDAC. In this context, the term “high-grade risk factor” refers to a referral criterion that warrants specialist evaluation when present alone rather than to a strictly defined epidemiological risk category. Patients are assessed by primary care physicians using predefined PDAC risk factors (Figure 1).

Figure 1. Referral pathway in the Hiroshima Pancreas Cancer Early Diagnosis With Collaboration and Examination (Hi-PEACE) project. CT: computed tomography; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; DUPAN-2: Duke pancreatic monoclonal antigen type 2; EUS: endoscopic ultrasonography; MRI: magnetic resonance imaging; PDAC: pancreatic ductal adenocarcinoma; Span-1: s-pancreas-1 antigen.



Low-grade risk factors include the following:

- Family history of PDAC in one first-degree relative
- Diabetes mellitus
- Obesity (BMI >30 kg/m^2)
- Smoking history
- Alcohol consumption of 37.5 g or more per day
- Abnormal pancreatic enzyme levels

Patients with 3 or more low-grade risk factors are considered eligible for referral.

Abnormal pancreatic enzyme levels are defined as serum levels of any pancreatic enzyme (amylase, pancreatic amylase, lipase, elastase, or trypsin) above the upper limit of normal at each participating institution. Because pancreatic enzyme measurements and their reference ranges may differ across institutions, abnormal values are defined using institution-specific reference ranges.

High-grade risk factors include the following:

- Family history of PDAC in 2 or more first-degree relatives
- New-onset diabetes mellitus or rapid worsening diabetes mellitus
- Elevated tumor marker levels

Patients with at least 1 high-grade risk factor are eligible for referral.

Elevated tumor marker levels are defined as serum levels of any pancreatic cancer–related tumor marker, including carcinoembryonic antigen, carbohydrate antigen 19-9, s-pancreas-1 antigen, or Duke pancreatic monoclonal antigen type 2, exceeding the upper limit of normal at each participating institution. Tumor marker elevation is used as a referral criterion rather than a diagnostic criterion for PDAC. New-onset diabetes mellitus is defined as diabetes mellitus diagnosed within 1 year before referral. Rapid worsening of diabetes mellitus is determined by the treating physician based on clinically apparent deterioration in glycemic control, with no predefined thresholds for glycated hemoglobin or blood glucose levels.

Imaging-Based Identification

Patients are also eligible for referral when abdominal ultrasonography, CT, or MRI performed during health checkups, surveillance, or follow-up for other conditions reveals suspicious pancreatic imaging findings. Such findings include a pancreatic mass, indirect findings suggestive of PDAC, or imaging findings suggestive of chronic pancreatitis. Indirect findings suggestive of PDAC include main pancreatic duct dilatation, main pancreatic duct stenosis, abrupt caliber changes, pancreatic cysts, and focal pancreatic parenchymal atrophy.

Diagnostic Evaluation at Core Hospitals

Patients identified using either pathway are referred to core hospitals for further assessment by pancreatic specialists. Diagnostic evaluation is performed in accordance with the Japanese Clinical Practice Guidelines for PDAC using CT, MRI, and EUS as the principal imaging modalities. Although the overall diagnostic workup is standardized according to the referral criteria and guideline-based evaluation, the specific diagnostic procedures and their sequence will be determined by the treating physicians based on each patient's clinical condition, imaging findings, and suspected disease stage. Endoscopic retrograde cholangiopancreatography (ERCP) and/or EUS-guided tissue acquisition (EUS-TA) may be performed when pathological confirmation is clinically indicated, particularly in patients with suspected PDAC without a definite mass lesion or in those requiring histological confirmation before treatment. The final diagnosis of PDAC is based on pathological findings when available or on a comprehensive clinical diagnosis using imaging findings, clinical course, and multidisciplinary assessment. If PDAC is diagnosed, subsequent treatment is determined in accordance with the Japanese Clinical Practice Guidelines for PDAC. Surgical resection is performed in patients with resectable disease, and neoadjuvant chemotherapy is considered when clinically indicated, whereas patients with unresectable disease receive systemic chemotherapy or other appropriate treatments.

Data Collection and Management

Clinical data are collected at core hospitals where pancreatic specialists are based and are subsequently centralized at Hiroshima University. Data are recorded using standardized Microsoft Excel–based case report forms distributed monthly by Hiroshima University and submitted to the university via encrypted email or secure file transfer. Information extracted from the medical records includes patient background, clinical features, blood test results, imaging findings, pathological findings, surgical findings, and prognosis.

To ensure data security and confidentiality, all case report forms are managed as password-protected files. Each participant is assigned an anonymized study ID, and directly identifiable personal information is not included in the database used for the analysis. Hiroshima University manages a centralized database, and access to the data is restricted to authorized study personnel. Data validation is performed by the coordinating center, and queries are issued to participating institutions when missing, inconsistent, or unclear data are identified.

Outcomes

The primary outcome is the number and proportion of participants diagnosed with early-stage PDAC, defined as stage 0 or I disease, among all participants referred to core hospitals through the Hi-PEACE project. Secondary outcomes include the number and proportion of participants diagnosed with PDAC overall, the proportion of early-stage PDAC among all diagnosed PDAC cases, the number and proportion of participants who underwent surgical resection among those diagnosed with PDAC, the distribution of PDAC risk factors among participants diagnosed with PDAC and among those diagnosed with early-stage PDAC, and the distribution and diagnostic yield of suspicious pancreatic imaging findings among referred participants. The diagnostic procedures performed at core hospitals, including CT, MRI, EUS, ERCP, and EUS-TA, as well as the clinical stage, treatment status, and prognosis of participants diagnosed with PDAC, are also assessed. To characterize the operation of the regional referral system, annual referral volumes and the distribution of referrals across participating core hospitals and secondary medical care areas will be evaluated descriptively.

Sample Size

The planned sample size is 25,000. Because this is a prefecture-wide prospective observational study with primarily descriptive objectives, the sample size is not based on formal statistical power calculations. Instead, it was determined based on the feasibility of participant enrollment, the expected annual number of referrals through the Hi-PEACE project, and prior experience with the Onomichi project. In the Onomichi project, 18,507 individuals were referred as suspected PDAC cases over a 20-year period, and 610 patients were diagnosed with PDAC. Although this project provides an important reference, direct extrapolation is limited because the observation period, medical care area, population size, and referral criteria differ from those of this study. On the basis of the anticipated referral volume across Hiroshima Prefecture, approximately 4000 participants are expected to be enrolled annually, resulting in a target sample size of 25,000 participants during the planned enrollment period. This sample size was considered appropriate for describing the feasibility of the prefecture-wide referral system and for evaluating the clinical characteristics, diagnostic pathways, and outcomes of patients with PDAC detected through the Hi-PEACE project.

Statistical Analysis

Statistical analyses will be performed using JMP Pro (version 18.0.0; JMP Statistical Discovery LLC). Baseline participant characteristics will be summarized using descriptive statistics. Continuous variables will be reported as medians with IQRs, as appropriate, and categorical variables will be presented as counts and percentages.

The primary outcome is defined as the number and proportion of participants diagnosed with early-stage PDAC (stages 0 and 1) among all participants referred to core hospitals through the Hi-PEACE project; these outcomes will be reported with 95% CIs. The overall PDAC detection rate will also be calculated and reported with 95% CIs. The proportion of early-stage PDAC among all diagnosed PDAC cases will be summarized descriptively.

To characterize the operation of the regional referral system, annual referral volumes and the distribution of referred participants across participating hospitals and secondary medical care areas will be summarized descriptively. Annual trends in overall PDAC detection rates and the proportion of stage 0 or I PDAC among diagnosed PDAC cases will also be evaluated. As enrollment began in November 2022, data from 2022 will be treated as a partial year when evaluating annual trends.

No formal historical control group was included in the original study design. An exploratory comparison with preimplementation data from participating institutions, including referral volumes and PDAC detection outcomes, may be considered if sufficiently complete and comparable historical data become available and any necessary approvals are obtained.

The distribution of PDAC risk factors and suspicious pancreatic imaging findings will be summarized for all referred participants, participants diagnosed with PDAC, and participants diagnosed with early-stage PDAC. For each referral criterion and imaging finding, the diagnostic yield is calculated as the proportion of participants diagnosed with PDAC among those meeting the corresponding criterion. Diagnostic procedures performed at the core hospitals, including CT, MRI, EUS, ERCP, and EUS-TA, will be summarized descriptively.

When comparisons are performed, continuous variables will be compared using the Wilcoxon rank-sum test, whereas categorical variables will be compared using the chi-square test or Fisher exact test, as appropriate. Comparisons will include participants with PDAC vs those without it and those with early-stage PDAC vs those with advanced-stage PDAC. Factors associated with PDAC detection and early-stage

PDAC detection will be evaluated using logistic regression analysis. Candidate variables will include demographic characteristics and clinically relevant factors such as diabetes mellitus, smoking history, pancreatic cysts, main pancreatic duct abnormalities, abnormal pancreatic enzyme levels, and other referral criteria. Variables included in the multivariable models will be selected based on clinical relevance and findings from previous studies, with care taken to avoid overfitting and multicollinearity. The results will be expressed as odds ratios with 95% CIs.

Missing data will be reported for each variable. Analyses will be conducted using available data, and no imputation is planned for the primary analysis. If the extent of missing data is substantial for key variables, the potential influence of missingness will be assessed in sensitivity analyses or considered when interpreting the results. Statistical significance is set at a 2-sided $P<.05$.

Ethical Considerations

This study is being conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hiroshima University, which serves as the lead institution (approval E2023-0100). Ethical approval was also obtained from the ethics committees of all participating institutions. Because this is a prospective observational study using data collected during routine clinical practice, the ethics committees waived the requirement for written informed consent. Study information is made publicly available at each participating institution, and eligible participants are given the opportunity to opt out of having their data used.

To protect participants' privacy, personally identifiable information, including names and dates of birth, is removed from data extracted from medical records. Each participant is assigned a study-specific anonymized ID, and only deidentified data are used for the analysis. The correspondence table linking personal identifiers and study IDs is managed securely by the designated data manager and stored separately in password-protected files on computers not connected to external networks. Deidentified study data are stored on computers not connected to external networks. When external storage media are used, devices with security functions are stored in locked cabinets. Study data will be retained for 5 years after study completion or 3 years after the final publication of the study results, whichever occurs later. After the retention period, paper documents will be shredded or dissolved, and electronic files will be securely deleted.

Dissemination of Results

The findings of this multicenter observational study will be published in peer-reviewed scientific journals and presented at national and international conferences. Results will be reported in aggregated statistical form so that no individual information will be identifiable.

Results

Participant enrollment began on November 20, 2022, and is planned to continue until December 31, 2028. As of the data cutoff date (December 31, 2025), 9866 participants had been enrolled through the Hi-PEACE project. The overall study period is planned to last until December 31, 2030. The planned sample size is 25,000 participants, and data collection and analysis are ongoing.

Discussion

Principal Considerations

This manuscript presents the objective, design, and study protocol of Hi-PEACE, a prefecture-wide collaborative program for the early detection of PDAC in Hiroshima Prefecture. A key feature of this project is the systematic identification in primary care settings of individuals with PDAC risk factors or suspicious pancreatic imaging findings, followed by referral to core hospitals with pancreatic specialists.

The referral criteria were established based on PDAC relative risks described in the Japanese Clinical Practice Guidelines for PDAC and findings from previous studies of early-stage PDAC (Table 1) [3,4,8,9]. Previous studies have reported that diabetes mellitus, pancreatic cysts, smoking history, and heavy alcohol consumption are present in approximately 30% of patients with early-stage PDAC [4]. Moreover, abnormal pancreatic enzyme levels have been reported in approximately half of these cases [4]. In addition, early-stage PDAC is often detected not through direct visualization of a pancreatic mass but through indirect pancreatic imaging findings, such as main pancreatic duct dilatation, pancreatic duct stenosis, and pancreatic cysts. Accordingly, the Hi-PEACE project incorporates both risk factor– and imaging-based pathways, placing particular emphasis on indirect imaging findings, to identify individuals who may warrant further pancreatic evaluation in routine clinical practice.

Table 1. Risk factors for pancreatic ductal adenocarcinoma (PDAC) according to the Japan Pancreas Society [9].

Category and factor	Risk level
Family history	
Family history of sporadic PDAC	• One first-degree relative with PDAC: 1.5-1.7–fold
Familial pancreatic cancer	• One first-degree relative: 4.5-fold

Category and factor	Risk level
	• Two relatives: 6.4-fold • Three or more relatives: 32-fold
Lifestyle factors	
Smoking	• 1.7-1.8–fold
Alcohol consumption	• 1.1-1.3–fold; alcohol intake of 24-50 g/d
Diabetes mellitus	• 1.7-1.9–fold • New-onset: 5.4-fold • 2 y after diagnosis: 1.5-1.6–fold
Obesity	• 1.3-1.4–fold
Pancreatic disease	
Pancreatic cyst	• 3.0-22.5–fold
MPD[a] dilatation	• 6.4-fold; MPD diameter ≥2.5 mm

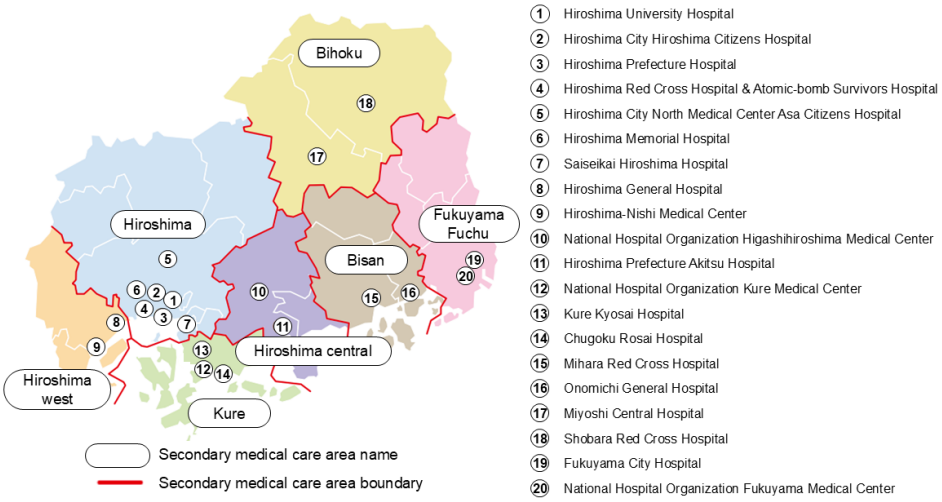
[a]MPD: main pancreatic duct.

Early-stage PDAC is often asymptomatic and remains difficult to detect in routine clinical practice [3,4]. Therefore, a strategy focusing on individuals with clinical risk factors or abnormal pancreatic imaging findings may be more feasible than population-based screening of the general population. In this context, the Hi-PEACE project is expected to clarify whether structured collaboration among primary care physicians, local medical associations, administrative bodies, and specialist centers can facilitate the detection of stage 0 and I PDAC.

Comparison With Prior Work

The Hi-PEACE project was developed based on the clinical experience and diagnostic concepts established in the Onomichi model, which suggested that ultrasonographic screening of individuals with PDAC risk factors, together with referral of patients with indirect pancreatic findings, may contribute to the detection of resectable PDAC [6]. Similar programs have been introduced in other municipalities in Japan [7]. Nevertheless, most previous programs were implemented at the municipal or regional level. In contrast, the Hi-PEACE project expands this framework to a prefecture-wide multicenter collaboration system spanning multiple secondary medical care areas. In Hiroshima Prefecture, pancreatic specialists are available in each secondary medical care area, allowing coordinated referral and collaboration between primary care physicians and pancreatic specialists to be completed within each area (Figure 2). This health care structure may make it feasible to implement a standardized referral system across the entire prefecture. Furthermore, this broader framework may provide useful information on the feasibility of expanding early detection programs beyond a single city or limited region. The Hi-PEACE project may also provide a model for coordinated regional health care delivery aimed at early PDAC detection, particularly in regions where pancreatic specialists are distributed across secondary medical care areas. Such an approach may provide a scalable alternative to centralized screening models.

Figure 2. Core hospitals with pancreatic specialists across secondary medical care areas in Hiroshima Prefecture. Hiroshima Prefecture is divided into 7 secondary medical care areas, and pancreatic specialists are available in each area. This health care structure allows referral and collaboration between primary care physicians and pancreatic specialists to be completed within each secondary medical care area and may facilitate the implementation of a standardized referral system across the entire prefecture.



The findings may contribute to the development of a workable referral strategy for individuals at increased risk of PDAC. By collecting data on risk factors, imaging findings, diagnostic procedures, pathological findings, treatment status, and prognosis, this study may help clarify which clinical or imaging features are most useful for identifying patients with early-stage PDAC. Additionally, evaluation of the referral pathway may provide insights into how collaboration between primary care physicians and specialist centers can be optimized in routine clinical practice.

Strengths and Limitations

This study has several strengths. First, it is designed as a prospective multicenter observational study grounded in collaboration among the Hiroshima Prefecture Medical Association, administrative bodies, and specialist centers. Second, the program applies predefined referral criteria based on PDAC risk factors and suspicious pancreatic imaging findings. The inclusion of indirect imaging findings in particular may help identify patients with early-stage PDAC before a definite pancreatic mass becomes apparent. Third, data are centralized at Hiroshima University, enabling systematic evaluation of referral pathways, diagnostic findings, treatment status, and clinical outcomes.

This study has some limitations. First, because this is an observational study without a control group or a comparable preimplementation cohort, it cannot directly establish whether the Hi-PEACE project improves early-stage PDAC detection or long-term clinical outcomes. Although annual trends in referral activity and diagnostic outcomes will be evaluated, observed changes cannot be attributed solely to the program. Future comparisons with historical data from participating hospitals, cancer registries, or previous regional early detection programs may provide useful context for interpreting the findings. In particular, an exploratory before-and-after comparison may be considered if sufficiently complete and comparable preimplementation data can be obtained. However, differences in patient populations, referral criteria, staging systems, and diagnostic practices should be considered when interpreting such comparisons. In addition, the Onomichi model had already been established in part of Hiroshima Prefecture before the introduction of Hi-PEACE. Second, although predefined referral criteria are used, referral practices and diagnostic approaches may vary among primary care physicians and participating institutions. Furthermore, because data on individuals who meet the referral criteria but are not referred are not collected, the program's reach among all eligible individuals cannot be fully assessed. Third, the number of patients with stage 0 or stage I PDAC may be limited despite the large planned sample size because early-stage PDAC is uncommon. Fourth, selection bias may exist because participants are identified through medical visits, health checkups, surveillance, or imaging performed for other conditions rather than through population-based screening. Finally, although prognostic information is included in the study data, sufficient long-term follow-up may not be available for all patients. Future analyses with extended follow-up may allow evaluation of overall survival among patients diagnosed with PDAC through the Hi-PEACE project. However, the present study does not include all patients diagnosed with PDAC in Hiroshima Prefecture, and assessing the impact of the project on prefecture-wide survival would require additional population-based data and an appropriate comparative study design. Potential biases, including lead-time bias, should also be considered when interpreting survival outcomes.

Conclusions

The Hi-PEACE project is a prospective prefecture-wide collaborative program designed to promote early PDAC detection through risk factor– and imaging-based referrals from primary care physicians to specialist centers. This study will provide information on the operation and diagnostic yield of a regional referral system, particularly for the detection of stage 0 and I PDAC. The findings may help inform the development of similar regional early detection programs, while further comparative studies and long-term follow-up will be needed to evaluate their impact on clinical outcomes.

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Generative AI Use

The authors declare that generative AI was used in the creation of this manuscript. Generative AI tool ChatGPT (GPT-5.5; OpenAI) was used for translation and proofreading, editing, or language polishing. The authors verified all outputs of the tool used in the preparation of this manuscript and take full responsibility for the final content of the manuscript.

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Data Availability

The datasets generated and/or analyzed in this study are not publicly available because of patient privacy restrictions. After study completion, deidentified data may be available from the corresponding author on reasonable request subject to institutional policies and ethics approval.

Authors' Contributions

Conceptualization: JI, YI

Data curation: JI, KH, KT, NE, YH, TU, TS, YF, TO, AY, MS, KH, BN, MK, T Minami, AO, MY, YN, T Mouri, EM, RK, YK, KT
Formal analysis: JI
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Methodology: JI, YI
Project administration: YI
Supervision: YI, SO
Writing—original draft: JI
Writing—review and editing: YI, SO
All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CT: computed tomography
ERCP: endoscopic retrograde cholangiopancreatography
EUS: endoscopic ultrasonography
EUS-TA: endoscopic ultrasonography–guided tissue acquisition
Hi-PEACE: Hiroshima Pancreas Cancer Early Diagnosis With Collaboration and Examination
MRI: magnetic resonance imaging
PDAC: pancreatic ductal adenocarcinoma

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