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Original article

Telomerase activity in pancreatic juice differentiates pancreatic cancer from chronic pancreatitis: A meta-analysis

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ABSTRACT

Background/objective: To evaluate the usefulness of genetic markers in pancreatic juice (PJ), and the combination of these markers with telomerase activity in the differential diagnosis of pancreatic ductal adenocarcinoma (PDAC) from chronic pancreatitis.
Methods: We conducted a meta-analysis for the diagnostic utility of the four major altered genes in PDAC (*KRAS*, *CDKN2A/p16*, *TP53*, and *SMAD4/DPC4*), telomerase activity, and a combination assay using PJ samples. A literature search was conducted in MEDLINE, Cochrane Library, and Web of Science. Data were pooled and presented as diagnostic sensitivity and specificity with 95% confidence intervals (CIs).
Results: Thirty-nine studies fulfilled the inclusion criteria. Pooled estimates of *KRAS* analysis were as follows: sensitivity was 0.67 (95% CI, 0.63–0.71) and specificity, 0.82 (95% CI, 0.79–0.85). For telomerase activity analysis, sensitivity was 0.82 (95% CI, 0.76–0.87) and specificity, 0.96 (95% CI, 0.90–0.99). The other three tumor suppressors demonstrated low sensitivity. The data did not suggest any publication bias. A combined analysis of *KRAS* and telomerase activity showed a higher diagnostic sensitivity (0.94; 95% CI, 0.83–0.99) than *KRAS* alone. A combined analysis of telomerase activity and cytology revealed more reliable diagnostic accuracy than telomerase activity alone, with high sensitivity (0.88; 95% CI, 0.74–0.96) and specificity (1.00; 95% CI, 0.91–1.00).
Conclusions: The most reliable marker in PJ samples for diagnosis of PDAC was telomerase activity. Telomerase activity can play a central role in diagnostic analysis using PJ samples, and can increase diagnostic accuracy when combined with *KRAS* mutations or cytological examination.
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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal neoplastic diseases. Despite the advances in diagnostic modalities, surgical techniques, chemotherapeutic agents or regimens, and perioperative multimodality therapies such as a combination of surgical resection and chemo-radiotherapy, the expected survival is still far from satisfactory [1,2]. It is widely acknowledged that early diagnosis and subsequent resection at an early stage can improve the survival rate of PDAC patients. Development of methods for early detection of PDAC is therefore necessary and urgent.

As one of the strategies for the early detection of PDAC, careful follow-up efforts currently focus on high-risk groups with syndromic or familial risk of PDAC, such as age, obesity, smoking, diabetes, and chronic pancreatitis (CP) [3]. The detailed mechanisms for PDAC development in CP patients have not been fully elucidated. Ductal epithelial hyperplasia, metaplasia and dysplasia, and *KRAS* gene mutations have been described in CP patients, suggesting an oncogenetic multistep sequence [4]. Although PDAC patients derived from high-risk groups are rather few compared to sporadic PDAC patients, the intensive and careful

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follow-up of individuals with CP can enable early detection of PDAC and reduce PDAC-specific mortalities. However, on the basis of current imaging criteria, PDAC remains difficult to distinguish from CP especially at the early stage because both demonstrate the similar imaging findings associated with the narrowing of main pancreatic duct.

Examination of pancreatic juice (PJ) may provide important information for early diagnosis of PDAC. As conventional PDAC originates from pancreatic ductal epithelial cells, genetic and cytological analysis using exfoliated ductal epithelial cells and secreted protein in PJ samples can be useful for the early detection of malignancy [5]. In terms of specific genetic alteration of PDAC, PDAC is unique because its genetic mutations are relatively limited to these four major genes: *KRAS*, *CDKN2A/p16*, *TP53*, and *SMAD4/DPC4* [6]. Therefore, analysis of these four major genetic markers may contribute to the early diagnosis of PDAC. In particular, *KRAS* oncogene is the most frequently acquired genetic alteration in PDAC, and it can be detected early in pancreatic carcinogenesis. However, various studies have demonstrated that the diagnostic utility of the *KRAS* gene mutation in various samples, including PJ samples, has limitations and heterogeneous results [7–9]. One of the significant limitations with *KRAS* mutation is its low specificity for PDAC diagnosis, because the mutations in *KRAS* are also detected in benign pancreatic diseases such as CP [7,10]. Therefore, more sensitive and specific methods for detection of genetic alterations are required for the differential diagnosis of PDAC from CP using PJ samples. However, it remains unclear whether a combination assay for genetic alterations in the four major genes or a combination of *KRAS* mutation analysis with conventional cytological examinations could improve the diagnostic accuracy for PDAC.

In addition to a combination assay of the four major genetic markers for PDAC diagnosis using PJ samples, we also investigated and analyzed telomerase activity. Telomerase is a key enzyme in the immortalization of malignant cells, and its increased activity has been detected in 85–90% of human cancers [11–13]. In humans, the active telomerase enzyme is composed of at least two major subunits: hTERT (human telomerase reverse transcriptase), which acts as enzyme's catalytic subunit, and hTR, which contains the template for reverse transcription [13]. Previous studies reported the activation of telomerase and overexpression of hTERT mRNA in PDAC [14–16]. Therefore, telomerase could potentially be used as an additional and independent marker for the detection of PDAC in PJ samples.

We conducted a meta-analysis of diagnostic accuracy studies on the differential diagnosis of PDAC from CP using PJ samples and validated the diagnostic utility of the four major genes and their combination assay.

Methods

This rigorous meta-analysis was performed in accordance with the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17].

Literature search strategy

A computerized search in MEDLINE (searched through PubMed), Cochrane Library, and Web of Science database was conducted to find relevant original publications on the accuracy of PDAC diagnosis using PJ samples. In brief, the search query comprised a combination of the following terms: “pancreatic cancer/adenocarcinoma/tumor/neoplasm” and “genetic marker/molecular marker/gene expression/mutation” and “pancreatic juice/fluid” and “sensitivity/specificity/accuracy/diagnosis.” Two authors (TH and MI) independently screened the search results based on the titles and abstracts. The full text of selected articles was reviewed to determine inclusion. The original search was conducted in September 2014 and the last update on December 20, 2014. References in all relevant publications were manually searched for additional studies overlooked using this search strategy. This method of cross-referencing was continued until no further relevant publications were identified. Additional records were found through a review of the full text and assessed for eligibility.

Inclusion criteria

Studies demonstrating the sensitivity and specificity of PDAC diagnosis based on the alteration of four major genes (*KRAS*, *TP53*, *CDKN2A/p16*, and *SMAD4/DPC4*) and telomerase activity in PJ samples were included. Studies were also restricted to those on human subjects, publication in the English language, and results reported in sufficient detail to construct the diagnostic 2×2 tables for each index test and the reference standards consisting of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN). Multiple publications from the same institute and authors were included only when no patient overlap was inferred based on the different periods of patient selection and the methods of mutation analysis. For publications from the same institutions and authors in an overlapping study period, only the publication with the most detailed study design or the largest sample size was included.

Exclusion criteria

Exclusion criteria were: (a) non-English language publications; (b) case reports; (c) review articles, editorials, letters, comments, and conference abstracts; (d) studies with insufficient data to construct the diagnostic 2×2 table; (e) studies reported from the same research group with a partially overlapping time period, which may have potential patient overlap; (f) studies with a sample size smaller than 10 patients; (g) studies involving patients with intraductal papillary mucinous neoplasm (IPMN)-derived invasive cancer; (h) studies using samples not originating from pure pancreatic fluid, such as those containing duodenal fluid, bile juice, and aspirated pancreatic cystic fluid; and (i) studies not within the field of interest of this study, such as comprehensive studies, studies about newly identified markers, and imaging analyses.

Data extraction

Two authors (TH and MI) extracted data on the authors, year of publication, sample size, technical analytic methods for each marker, sample preparation method of PJ, and actual number of TP, FP, FN, and TN cases from each of the studies. In some studies with multiple different index tests or sample preparations for the same target, data were extracted for each index test. As a control and counterpart for differential diagnosis, only CP patients were selected to avoid a massive selection bias resulting from heterogeneous pancreatic neoplasms such as pancreatic neuroendocrine tumor, IPMN, serous cystic neoplasms, and mucinous cystic neoplasms with a wide range of malignant potential.

Quality assessment

For the studies fulfilling the inclusion criteria, the methodological quality of each study was evaluated with the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist recommended by the Cochrane collaboration. The QUADAS-2 checklist consists of four domains including patient selection,

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