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Genetic Markers of Malignant Transformation in Intraductal Papillary Mucinous Neoplasm of the Pancreas:

A Meta-Analysis

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Abstract

Objectives—The objective of this study was to determine the relationship between specific genetic alterations and malignant transformation in intraductal papillary mucinous neoplasm (IPMN) of the pancreas.

Methods—Quantitative meta-analysis was conducted of studies through October 2010 that adhered to the 1996 World Health Organization guidelines for distinguishing adenoma and borderline IPMN versus carcinoma in surgically resected specimens using a random-effects model. We developed a 6-point scoring system to assess study quality.

Results—Thirty-nine studies (1235 IPMN samples) satisfied the inclusion criteria, and we conducted pooled analysis of 8 genetic markers: *MUC1*, *MUC2*, *MUC5AC*, *kRas*, *p53*, *hTERT* (human telomerase reverse transcriptase), *cyclooxygenase 2*, and *Shh* (Sonic hedgehog). Markers having the strongest association with malignant IPMN were *hTERT* (odds ratio [OR], 11.4; 95% confidence interval [CI], 3.5–36.7) and *Shh* (OR, 6.9; 95% CI, 2.4–20.2), whereas *MUC5AC* (OR, 1.0; 95% CI, 0.1–13.9) and *kRas* (OR, 2.0; 95% CI, 1.0–4.3) showed weak association with IPMN histologic progression.

Conclusions—Expression of *hTERT* is strongly associated with malignant transformation in IPMN, consistent with up-regulation of *hTERT* as a key step in progression of IPMN to cancer. Expression of *kRas* and *MUC5AC* is common but not strongly associated with IPMN histologic progression. The quality criteria used here may guide future reporting of genetic markers related to malignant transformation of IPMN.

Keywords

telomerase; mucin; pancreatic cancer; intraductal papillary mucinous neoplasm; IPMN; Sonic hedgehog; cyclooxygenase 2; p53; *hTERT*; *Cox2*; *kRas*; marker

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Intraductal papillary mucinous neoplasms (IPMNs) describe papillary proliferations of the exocrine pancreas epithelium that secrete copious amounts of thick mucin causing cystic dilatation of the ducts.[1] Since the pathologic entity was first described by Ohashi et al in 1982 and designated *intraductal papillary mucinous neoplasm* by Sessa et al[2] in 1994, it has been characterized radiologically, histologically, and molecularly and is thought to represent a lesion that is distinct from and less clinically aggressive than ductal adenocarcinoma.[3–5]

Histologic analysis of IPMN samples reveals a spectrum of progressive cytoarchitectural atypia. The spectrum of this histologic progression is reflected in the 1996 World Health Organization (WHO) classification of IPMN into 3 categories based on increasing nuclear atypia and mitotic rate: adenoma (IPM-A), borderline (IPM-B), and carcinoma (IPM-C, both in situ and invasive).[6] The histologic progression of IPMN from a benign (IPM-A or IPM-B) into a malignant (IPM-C) lesion has a significant impact on patient survival. In patients who underwent pancreatic resection between 1990 and 2007, the 5-year survival rate of patients with benign IPMN ranged from 89% to 95% versus 63% to 65% for patients with malignant IPMN.[7–9] Moreover, malignant transformation is not rare: the frequency of malignancy in IPMNs in the main pancreatic duct ranges from 60% to 92% in various reports.[10–15]

A longstanding question has been whether the histologic progression of IPMN reflects an accumulation of genetic mutations leading to increasing atypia. Many studies have therefore sought to identify specific genetic mutations associated with malignant transformation in IPMN. The objective of the present study was to enhance our understanding of malignant progression in IPMN based on literature published to date. Specifically, our aim was to perform a quantitative meta-analysis of studies from the past 14 years to determine the relationship between individual genetic alterations and malignant transformation in IPMN.

METHODS

Search Methods and Study Selection Criteria

A computerized literature search was performed independently in the PubMed (National Library of Medicine, Bethesda, Md), Cochrane Library, and EMBASE databases by 2 of the authors (S.N., G.E.I.). To identify studies investigating gene expression in IPMN, we used the following search terms: “intraductal papillary mucinous neoplasm,” “IPMN,” “intraductal papillary mucinous tumor,” “IPMT,” “IPMA,” “IPMB,” “IPMC,” “gene expression,” “molecular marker,” “*Ras*,” “*p53*,” “*MUC*,” “telomerase,” and “mutations.” Bibliographies from relevant publications were further reviewed to identify additional published articles not indexed by the major databases.

Studies published from January 1996 to October 2010 were potentially eligible for inclusion based on publication of WHO guidelines for classification of IPMN in 1996.[1] For the present meta-analysis, we included studies that satisfied the following criteria: (1) human subjects, (2) histologic confirmation of IPMN in surgically resected tissue, (3) classification of IPMN in accordance to WHO guidelines, (4) inclusion of data regarding genotype frequency and/or risk estimates, and (5) use of validated molecular methods for genotyping.

Individual case reports, editorials, review articles, and duplicate publications were excluded. We further excluded studies that incorporated patients with chronic pancreatitis, bile duct IPMN, and high-risk familial cohorts.

Data Extraction

Data were extracted independently by each reviewer using a standardized data abstraction form. Any disagreements between the 2 reviewers were examined by all 3 investigators and resolved by consensus.

Data Synthesis

The primary outcome was defined as IPMN with presence of malignant transformation (IPM-C). During the initial phase of data extraction, IPMN grade was extracted as presented in the original publication. For purposes of the present meta-analysis, IPMN grade was further dichotomized to either benign (IPM-A, IPM-B) or malignant (IPM-C) lesions.

Assessment of Study Quality

There is currently no validated method to rate the quality of observational studies on IPMN. To provide a means to appraise the methodologic quality of studies included in the present meta-analysis, we formulated a scoring system based on recommendations from the STROBE[16] and PRAISE guidelines.[17] This checklist consisted of 6 factors summarized in Figure 1A: review of histologic classification of IPMN, in the case of dysplasia or carcinoma review of histology by at least 2 independent pathologists, an explicit definition of genetic assay positivity, blinded genetic assay, description of statistical analysis, and mention of potential sources of bias. One point was assigned for the presence of each of the individual factors.

Statistical Analysis

Effect size was expressed as an odds ratio (OR) with the corresponding 95% confidence interval (CI). Quantitative meta-analysis was performed when 3 or more studies evaluated the same gene candidate. In the meta-analysis, pooled ORs were generated based on the individual studies using a random-effects model (DerSimonian and Laird) chosen based on the ability to incorporate between-study variance potentially related to differences among the populations included among studies. The I^2 test was used to evaluate study heterogeneity. For genetic markers with 5 or more studies, we performed further subgroup analyses based on methodologic quality (high quality, ≥ 3 points). Analyses were performed using Quantitative Meta-analysis version 2.2 (Biostat, Englewood, NJ).

RESULTS

The computerized literature search yielded 253 studies. Abstracts of these studies were reviewed, and 119 studies were excluded for the reasons delineated in Figure 1B. A full manuscript review was performed on the remaining 134 studies, and 95 additional studies were excluded. The most common reasons for exclusion were studies totaling less than 3 for a particular gene marker and studies that did not stratify IPMN samples by histologic grade according to the1996 WHO guidelines.

A total of 39 studies between January 1996 and October 2010 (representing a total of 1235 IPMN samples) met our predetermined inclusion criteria (Table 1). A pooled analysis was performed to determine the risk of malignant transformation for each genetic marker. Results are summarized according to individual gene candidates.

MUC Expression

Mucins are large, heavily glycosylated proteins that are differentially expressed in epithelial cells of glandular tissues and various tumor types.[19,21,57] Of the 19 mucin genes identified, *MUC1*, *MUC2*, and *MUC5AC* genes have been most frequently characterized in the pancreas. Eleven studies with 417 IPMN samples reported *MUC* expression.[18–21,23–26,58] These studies examined *MUC* expression at the mRNA level by in situ hybridization[20] or at the protein level by immunohistochemistry (IHC).[18,19,21,23–26,58] Because the expression of different mucin genes appears to vary with grade of IPMN, we pooled studies according to analysis of the most frequently reported mucin genes: *MUC1*, *MUC2*, and *MUC5AC*. Figure 2 summarizes the individual ORs.

Eight studies representing a total of 322 IPMN samples examined the expression of *MUC1* by IHC.[18–25] *MUC1* was expressed in 8.6% (15/174) of IPM-A/B samples and 35.8% (53/148) of IPM-C samples. The pooled OR for MUC1 and malignant transformation was 5.9 (95% CI, 1.8–19.8). Grouped according to study quality, high-quality studies' pooled OR was 3.6 (95% CI, 0.4–32.1), whereas low-quality studies' pooled OR was 7.4 (95% CI, 1.7–31.2).

Eight studies representing a total of 322 IPMN sample examined the expression of *MUC2* by IHC.[18–25] *MUC2* was expressed in 51.7% (90/174) of IPM-A/B samples and 68.9% (102/148) of IPM-C samples. The overall pooled OR for MUC2 and malignant transformation was 4.2 (95% CI, 1.7–10.1). Grouped according to study quality, high-quality studies' pooled OR was 14.5 (95% CI, 4.1–51.8), whereas low-quality studies' pooled OR was 1.3 (95% CI, 0.4–4.4).

Three studies representing a total of 231 IPMN samples examined the expression of *MUC5AC* by IHC.[20,24,26] Five studies were excluded from pooled analysis because all IPMN samples were positive for *MUC5AC*.[18,21,25,58,59] *MUC5AC* was expressed in 84.7% (149/176) of IPM-A/B samples and 92.4% (97/105) of IPM-C samples. The pooled OR for *MUC5AC* and malignant transformation was 1.0 (95% CI, 0.1–13.9).

Oncogenic *kRas* Expression

Activating point mutations in the GTP-binding protein kRas have been found in virtually all advanced pancreatic ductal adenocarcinoma and are thought to be an important step in pancreatic oncogenesis.[60] Thirteen studies representing a total of 285 samples examined the presence of the *kRas* oncogenic mutation by polymerase chain reaction (PCR) and sequencing[24,27–36,39,40] or IHC[29] on resected tissue. Figure 3 summarizes the individual ORs.

In pooled analysis, the oncogenic mutation in *kRas* was found in 48.3% (71/147) of IPM-A/B samples and 55.1% (76/ 138) of IPM-C samples. The pooled OR for *kRas* mutation and

malignant transformation was 2.0 (95% CI, 1.0–4.3). Grouped according to study quality, high-quality studies' pooled OR was 1.3 (95% CI, 0.4–4.2), whereas low-quality studies' pooled OR was 2.8 (95% CI, 1.1–7.1).

p53 Nuclear Expression

Most studies investigating p53 mutations in IPMN examined nuclear immunostaining of p53. This positivity criterion is based on the observation that wild-type p53 protein is present in the nucleus only at low levels, but mutant forms common to many types of cancer accumulate in the nucleus and can be visualized by IHC. Nuclear localization of p53 has been investigated as a prognostic factor in several kinds of gastrointestinal tumors including pancreatic cancer,[61] hepatocellular cancer,[62] colorectal cancer,[63] and gastric cancer.[64]

Six studies[24,41,42,44–46] measured p53 mutations according to recommendations by Kawai et al,[65] in which samples considered positive had greater than 10% of cells with positive nuclear immunostaining of p53. These 6 studies representing a total of 293 IPMNs identified positive p53 staining in 16.9% (31/183) of IPM-A/B samples and 40.9% (45/110) of IPM-C samples.[24,41,42,44–46] Three studies used a threshold of 5% positive cells to define positive p53 staining.[21,39,43] Together, these 3 studies examined 111 IPMN samples and identified positive staining in 17.1% (13/76) of IPM-A/B samples and 27.5% (11/40) of IPM-C samples.[21,39,43] Uemura et al[32] examined 15 IPMN samples and, using a criterion of focal aggregates of more than 30 cells with positive nuclear staining, found positive p53 staining in 0% (0/7) of IPM-A/B samples and 25% (2/8) of IPM-C samples. Ueda et al[23] examined 24 IPMN samples and found that no IPM-A/B samples had any p53-positive nuclear staining, but 27% (3/11) of IPM-C samples had scattered or diffuse positive cells. Mueller et al[31] performed PCR and single-strand conformation polymorphism analysis to find sequence changes in 13 IPMN samples and in this manner identified mutations in 10% (1/10) of IPM-A/B samples and 33.3% (1/3) of IPM-C samples. Wada et al[34] used fluorescence-labeled microsatellite markers to detect loss of heterozygosity in the 17p13 chromosomal locus of *p53* and found loss of heterozygosity in no IPM-A/B samples but in 66.7% (6/9) of IPM-C samples.

Pooling all the above studies examining p53 mutations by IPMN histologic grade, a total of 478 IPMN samples are examined, of which p53 mutations were identified in 14.9% (45/302) of IPM-A/B samples and 38.6% (68/176) of IPM-C samples. The pooled OR for p53 mutations and malignant transformation was 6.3 (95% CI, 2.9–13.8). Grouped according to study quality, high-quality studies' pooled OR was 3.5 (95% CI, 1.3–9.6), whereas low-quality studies' pooled OR was 15.6 (95% CI, 4.4–55.3). Figure 4 summarizes the individual ORs.

Telomerase Expression

The human telomerase reverse transcriptase (*hTERT*) gene encodes the catalytic component of telomerase required to overcome telomere shortening and cellular senescence. Therefore, activation of *hTERT* is considered a hallmark of cancer.[66,67] Three studies representing a total of 82 samples examined expression of *hTERT* by IHC[48,49] or reverse transcriptase–PCR[47] on resected tissue specimens (Fig. 5). *hTERT* expression was found in 23.7% (9/38)

of IPM-A/B samples and 88.6% (39/44) of IPM-C samples. The pooled OR for hTERT mutation and malignant transformation was 11.4 (95% CI, 3.5–36.7).

Cyclooxygenase 2 Expression

The biosynthesis of prostaglandins by the cyclooxygenase 2 (*Cox2*) enzyme is thought to mediate many properties of carcinogenesis. Expression of *Cox2* is upregulated in pancreatic cancer[68,69] and is thought to stimulate invasion[70] and angiogenesis.[71] Five studies representing a total of 158 IPMN samples examined the expression of *Cox2* by IHC (Fig. 5).[24,50–53] *Cox2* was expressed in 53.3% (48/90) of IPM-A/B samples and 75.4% (52/69) of IPM-C samples. The pooled OR for *Cox2* and malignant transformation was 2.9 (95% CI, 1.1–7.7). Grouped according to study quality, high-quality studies' pooled OR was 2.6 (95% CI, 0.6–11.9), whereas low-quality studies' pooled OR was 3.1 (95% CI, 0.9–11.1).

Shh Expression

The secreted factor Sonic hedgehog (*Shh*) has an important role in regulating normal pancreas development and has been implicated in tumorigenesis in pancreatic ductal adenocarcinoma.[72] Three studies representing a total of 136 IPMN samples examined the expression of *Shh* by IHC (Fig. 5).[54–56] *Shh* was expressed in 68.7% (57/83) of IPM-A/B samples and 90.6% (48/53) of IPM-C samples. The pooled OR for Shh expression and malignant transformation was 6.9 (95% CI, 2.4–20.2).

Heterogeneity and Impact of Quality

The estimated I^2 was low (<25%) for studies evaluating *telomerase*, *Cox2*, and *Shh*. Estimated I^2 for studies on *kRas* and *p53* was moderate, 32% and 36%, respectively. Estimated I^2 exceeded 50% for each of the MUC genes analyzed (*MUC1*, 54%; *MUC2*, 68%; and *MUC5AC*, 79%). Heterogeneity was significantly lower among high-quality studies of *MUC2* (I^2, 0%) and *MUC5AC* (I^2, 16%). However, this was not the case for *MUC1* (I^2 among high-quality studies, 63%).

DISCUSSION

We have performed a quantitative meta-analysis of genetic markers associated with histologic progression of IPMN. Through a computerized literature search of online databases using predetermined inclusion criteria, we identified 39 studies between January 1996 and October 2010 (representing a total of 1235 IPMN samples) that examined the expression of 8 different genetic markers in benign versus malignant IPMN: *MUC1*, *MUC2*, *MUC5AC*, *kRas*, *p53*, *hTERT*, *Cox2*, and *Shh*. Pooled analysis of these studies revealed expression of *hTERT*, *Shh*, and *MUC1* to have the strongest association with malignant progression of IPMN and expression of *MUC5AC* to have the weakest association with malignant progression of IPMN.

Intraductal papillary mucinous neoplasm of the pancreas has presented challenges in terms of pathophysiology and clinical management. Although the pathologic entity has been recognized for decades, the mechanisms of malignant transformation remain poorly understood. A key hypothesis has been that IPMN is fundamentally a genetic lesion and that

an accumulation of somatic mutations drives the histologic progression, ultimately leading to malignant transformation. This hypothesis is a basis for pursuit of genetic markers that can be utilized to improve diagnosis, guide optimal management, and potentially design new therapeutic targets. In this meta-analysis, we investigated the hypothesis that specific genetic alterations are associated with the histologic progression of IPMN.

The risk of cancer associated with various gene mutations ranged from 1.0 to 11.41. The marker found to have the strongest association with malignant IPMN was *hTERT* (OR, 11.4; 95% CI, 3.5–36.7). One interpretation of this finding is that the genetic alterations leading to abnormal expression of *hTERT* occur later in the histologic progression of IPMN toward cancer. This is consistent with the hypothesis of "telomere crisis" in carcinogenesis. This model postulates that telomeres are progressively shortened with cell proliferation until cells reach "crisis" at which point most cells will die; the ability of rare cells to overcome crisis by upregulating *hTERT* is a critical step in carcinogenesis.[66] Shortening of telomeres has been reported in some IPM-A but has been noted to progressively worsen with histologic progression.[49] Therefore, the dramatic upregulation of *hTERT* observed in malignant compared with benign IPMN supports the notion of a crisis point in the development of malignancy.[49]

In the pooled analysis, we also identified markers that had little or no association with malignant progression of IPMN. Although fairly common, *MUC5AC* and *kRas* were not strongly associated with malignancy among IPMN lesions. A weaker association with malignant progression may suggest that alterations leading to expression of these markers occur early in the histologic progression of IPMN toward cancer. Activating mutations of *kRas* are recognized to be among the earliest mutations leading to pancreatic cancer, detected in more than 40% of early pancreatic intraepithelial neoplasia lesions.[60,73,74] Alternatively, markers with no association with malignant IPMN may have no role in the pathobiology of IPMN progression. This could be the case with *MUC5AC*, which had no association (OR, 1.0; 95% CI, 0.1–13.9) as opposed to *MUC1*, which had a strong association (OR, 5.9; 95% CI, 1.8–19.8) with malignant transformation. *MUC5AC* is a secreted mucin speculated to form a protective gel around tumors,[75] a property that may be advantageous for all neoplasms, benign or malignant. In contrast, *MUC1* is a membrane-associated mucin that has been demonstrated to bind and signal through β-catenin and mitogen-activated protein kinase pathways critical in cell proliferation, and thus upregulation of *MUC1* may be necessary for the progression of IPMN from benign to malignant lesions.[76–78] Interestingly, a knockout of *Muc1* in mice significantly slowed the growth rate of oncogene-induced breast tumors and decreased the rates of tumor metastasis.[79]

A proposed model for genetic alterations associated with malignant progression of IPMN based on the present meta-analysis is presented in Figure 6. How well these ORs in fact correspond to the pathobiology of IPMN progression remains to be validated in future functional studies. A key question is whether the genetic markers are so-called "passenger" or "driver" alterations: do these genetic alterations cause IPMN lesions to acquire malignant behavior, or are they simply a consequence of other genetic alterations that in fact drive IPMN progression?

The strengths of the approach taken in this meta-analysis include a comprehensive and unbiased search of IPMN literature, the use of standardized systematic review and meta-analysis techniques using predefined inclusion and exclusion criteria, and elaboration of a scoring system to assess quality of included studies.

There were several limitations to the present study. In this meta-analysis, IPMN lesions were stratified according to the WHO IPM-A/B versus IPM-C grades, but insufficient data were available to stratify according to histologic cell type (eg, gastric, intestinal, pancreatobiliary, oncocytic). There are also potential biases derived from limiting our search to published studies. Unpublished data may have an increased proportion of null results in which no association is detected between a genetic marker and IPMN progression. The genetic markers eligible for pooled analysis were limited by the number of studies that met the inclusion criteria. A number of markers such as *p16*[23,43] and *Smad4*[80,81] have been frequently investigated but have not been used as consistent criteria for measuring genetic alterations. Additional candidate genetic markers that have been examined in IPMN tissue were unable to be included in the quantitative meta-analysis because of availability of fewer than 3 published reports in the medical literature. Finally, as it is derived from published reports, this meta-analysis is limited to previously characterized markers. Unbiased approaches such as RNASeq will be critical to identify novel genetic alterations that play a role in malignant progression of IPMN.

We developed a 6-point scoring system based on the STROBE[16] and PRAISE reporting guidelines[17] for observational studies. We found considerable variability in quality among the studies included in the present meta-analysis. In particular, many studies failed to confirm the histologic diagnosis of malignancy by 2 independent pathologists. In our analysis, we found that the risk of malignant transformation associated with a number of gene mutations varied according to study quality. Therefore, we advocate establishment of standardized quality reporting criteria to reduce heterogeneity and enhance accuracy of future studies evaluating genetic risk factors for malignant transformation of IPMN.

Ultimately, the motivation for this and future studies is to elucidate genetic markers that can improve diagnosis, guide optimal management, and offer new therapeutic targets. In addition, elucidating the genetic alterations underlying malignant transformation of IPMN may have relevance to pancreatic cancer. A recent meta-analysis identified *Cox2* as a marker associated with poor survival outcome in pancreatic cancer.[82] Here, we similarly find that *Cox2* expression is associated with malignant IPMN (OR, 2.9), highlighting potential parallels in the pathogenesis of malignant IPMN and pancreatic cancer.

In summary, numerous studies have evaluated candidate gene mutations associated with malignant transformation in IPMN. Using quantitative meta-analysis, we identified a strong association of *hTERT* expression with malignant transformation of IPMN, consistent with up-regulation of *hTERT* as a key step in progression of IPMN to cancer. Although *kRas* was a commonly detected mutation, its presence was not strongly associated with histologic progression of IPMN. In the context of this meta-analysis, we have also proposed a set of quality criteria for reporting of genetic studies related to malignant transformation of IPMN.

We believe the present findings can be used as a framework to help guide further research aimed at elucidating the genetic basis of malignant progression in IPMN of the pancreas.

Abbreviations

CI	confidence interval
Cox2	cyclooxygenase 2
OR	odds ratio
IPMN	intraductal mucinous neoplasm
hTERT	human telomerase reverse transcriptase
Shh	Sonic hedgehog
IHC	immunohistochemistry

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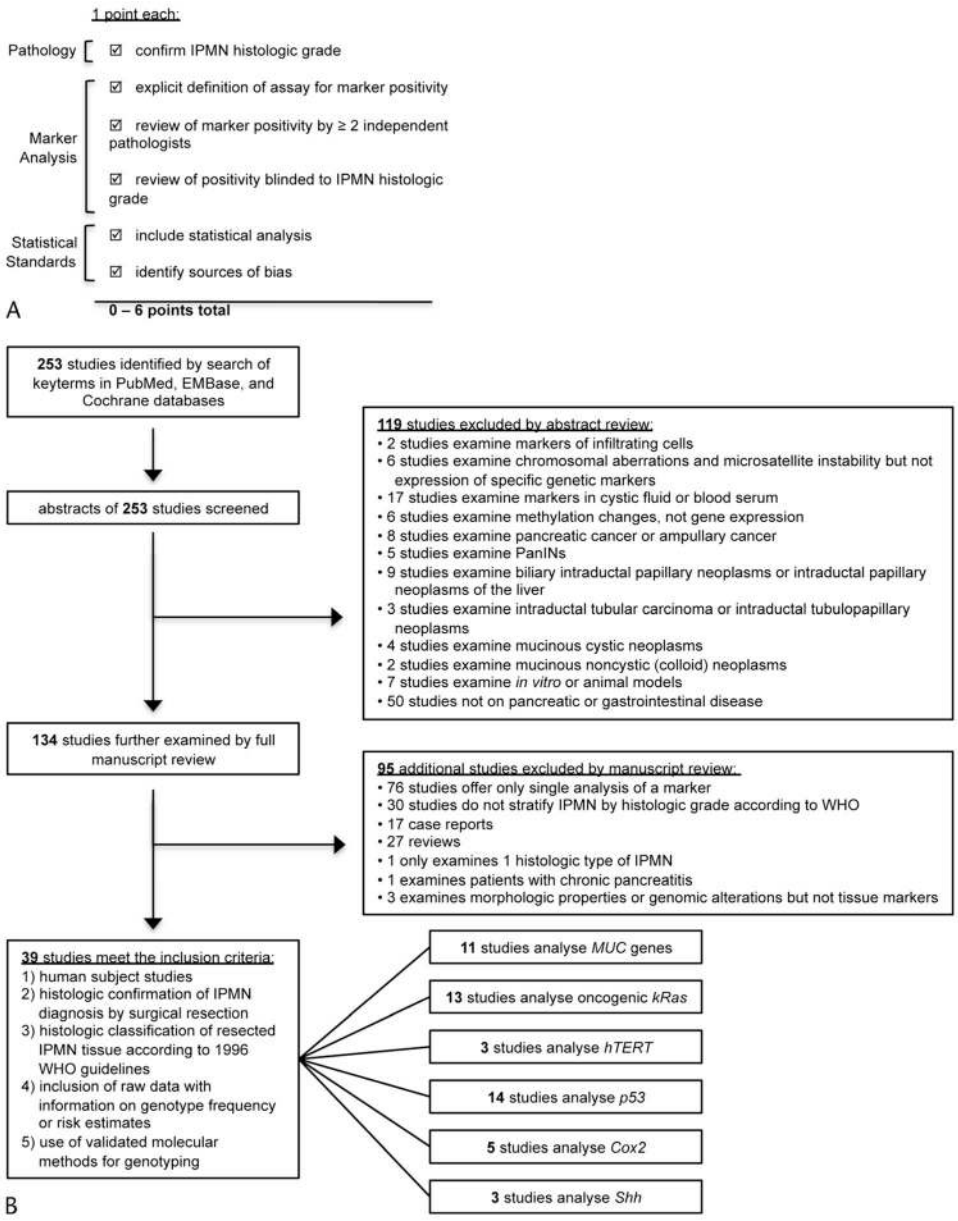

FIGURE 1.

Methodology used in this meta-analysis. A, We developed a 6-point scoring system to assess quality of studies based on recommendations from the STROBE[16] and PRAISE[17] guidelines. B, Flow diagram of the literature search and study selection.

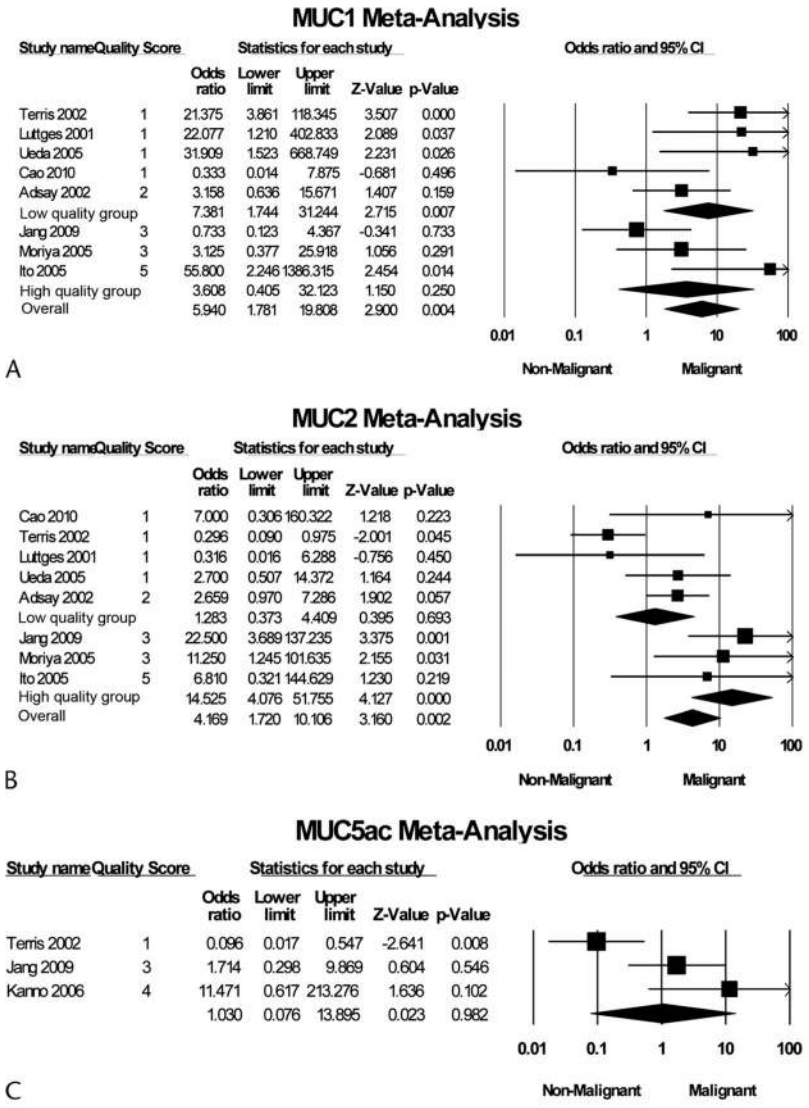

FIGURE 2.

Forest plot of studies examining association of *MUC1* (A), *MUC2* (B), or *MUC5AC* (C) expression and malignant transformation of IPMN. Methodologic quality of each study was assigned a score from 1 to 6 based on criteria summarized in Table 1. For each study, the quality score, OR; 95% CI, and relative weight are shown. The size of the data markers (squares) represents the statistical weight that each study contributed to the random-effects summary estimates; horizontal lines represent the 95% CI. The diamonds indicate the summary OR. I^2 test *P* values evaluating study heterogeneity are shown.

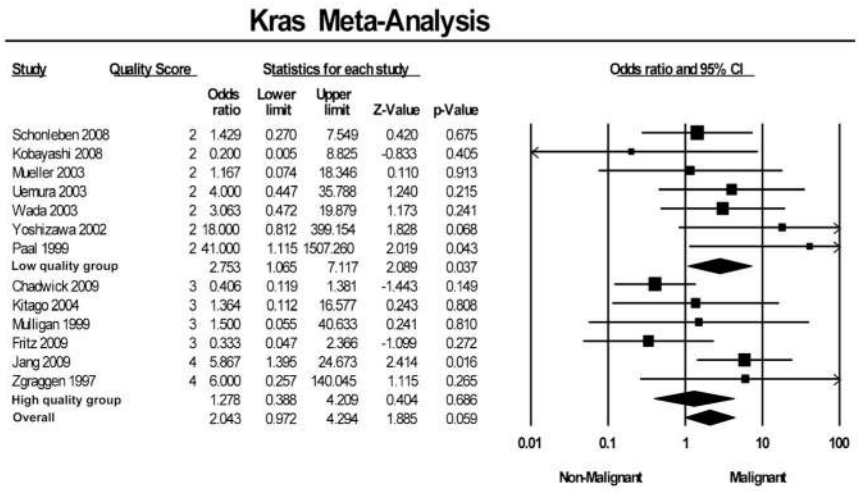

FIGURE 3.

Forest plot of studies examining association of *kRas* expression and malignant transformation of IPMN.

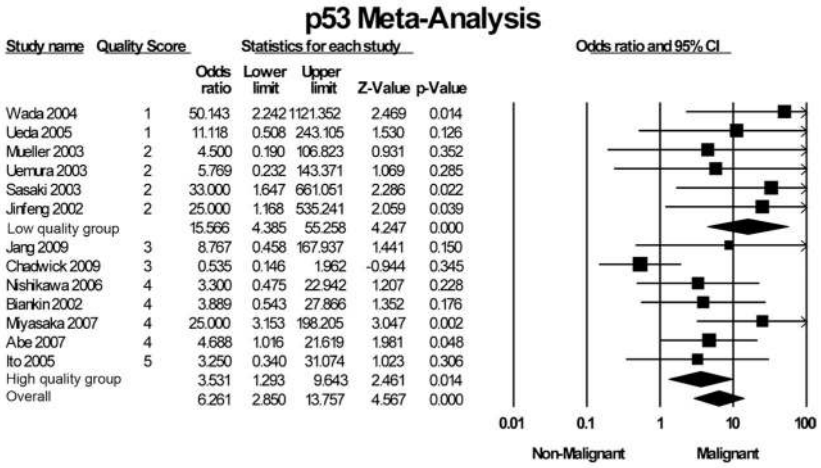

FIGURE 4.

Forest plot of studies examining association of altered *p53* expression and malignant transformation of IPMN.

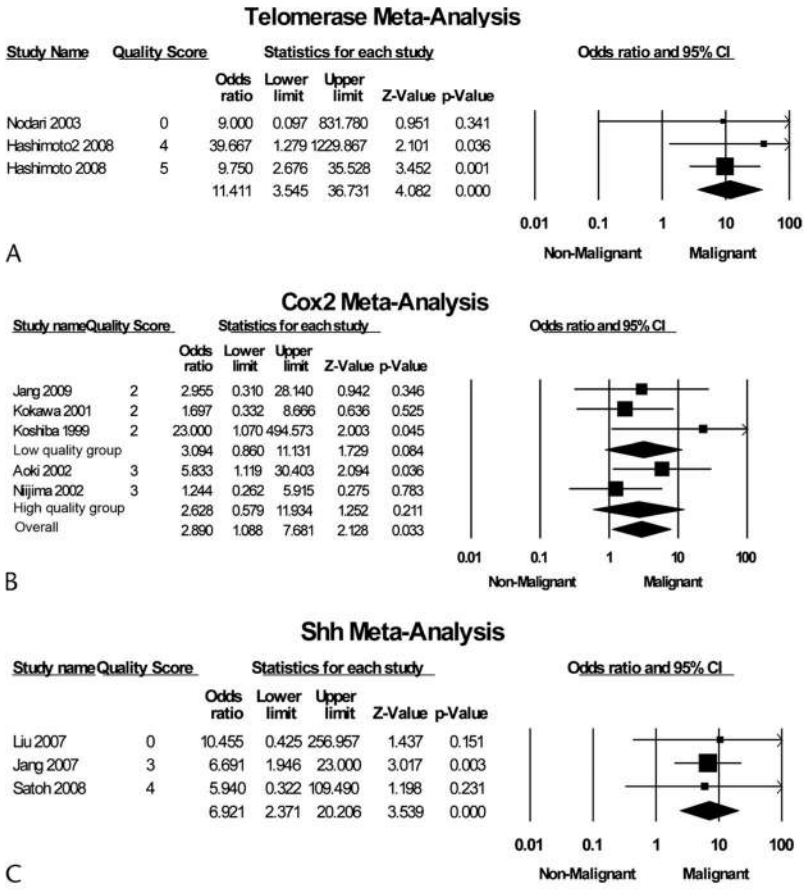

FIGURE 5.

Forest plot of studies examining association of *hTERT* (A), *Cox2* (B), or *Shh* (C) expression and malignant transformation of IPMN.

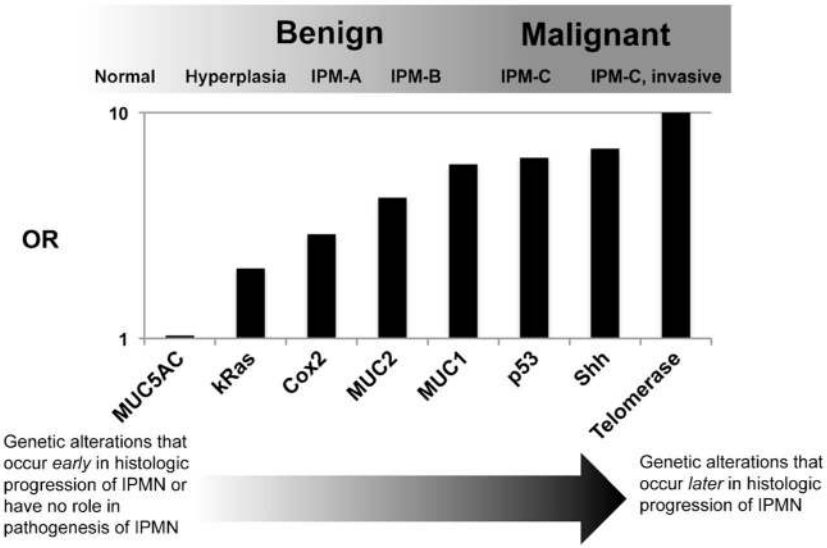

FIGURE 6.

A model for genetic alterations associated with malignant progression of IPMN based on the findings of this meta-analysis.

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TABLE 1

Studies Meeting Inclusion Criteria for Meta-Analysis Organized by Genetic Marker

First Author	Year	Total No. IPMNs	Study Area	Gene	Assay, Definition of Positivity	OR	95% CI	Study Quality (0–6)
Luttges et al[18]	2001	51	Germany, Italy, United States	*MUC1*	IHC	22.077	1.210–402.833	1
Adsay et al[19]	2002	74	United States	*MUC1*	>10% Cells positive by IHC	3.158	0.636–15.671	2
Terris et al[20]	2002	57	France	*MUC1*	IHC	21.375	3.861–118.345	1
Ito et al[21]	2005	21	Japan	*MUC1*	>5% Cells positive by IHC	55.8	2.246–1386.315	5
Moriya et al[22]	2005	37	Japan	*MUC1*	>10% Cells positive by IHC	3.125	0.377–25.918	3
Ueda et al[23]	2005	24	Japan	*MUC1*	IHC	31.909	1.523–668.749	1
Jang et al[24]	2009	41	South Korea	*MUC1*	>10% Cells positive by IHC	0.733	0.123–4.367	3
Cao et al[25]	2010	17	United States	*MUC1*	IHC	0.333	0.014–7.875	1
Luttges et al[18]	2001	51	Germany, Italy, United States	*MUC2*	IHC	0.316	0.016–6.288	1
Adsay et al[19]	2002	74	United States	*MUC2*	>10% Cells positive by IHC	2.659	0.970–7.286	2
Terris et al[20]	2002	57	France	*MUC2*	IHC	0.296	0.090–0.975	1
Ito et al[21]	2005	21	Japan	*MUC2*	>5% Cells positive by IHC	6.810	0.321–144.629	5
Moriya et al[22]	2005	37	Japan	*MUC2*	>10% Cells positive by IHC	11.250	1.245–101.635	3
Ueda et al[23]	2005	24	Japan	*MUC2*	IHC	2.700	0.507–14.372	1
Jang et al[24]	2009	41	South Korea	*MUC2*	>10% Cells positive by IHC	22.500	3.689–137.235	3
Cao et al[25]	2010	17	United States	*MUC2*	IHC	7.000	0.306–160.322	1
Terris et al[20]	2002	57	France	*MUC5AC*	IHC	0.096	0.017–0.547	1
Kanno et al[26]	2006	51	Japan	*MUC5AC*	IHC	11.471	0.617–213.276	4
Jang et al[24]	2009	41	South Korea	*MUC5AC*	>10% Cells positive by IHC	1.714	0.298–9.869	3
Z'graggen et al[27]	1997	16	United States	*kRas*	Sequence mutation	6.000	0.257–140.045	4
Mulligan et al[28]	1999	7	United States	*kRas*	Sequence mutation	1.500	0.055–40.633	3
Paal et al[29]	1999	22	United States	*kRas*	Immunohistochemistry	41.000	1.115–1507.260	2
Yoshizawa et al[30]	2002	7	Japan	*kRas*	Sequence mutation	18.000	0.812–399.154	2
Mueller et al[31]	2003	13	Germany	*kRas*	Sequence mutation	1.167	0.074–18.346	2
Uemura et al[32]	2003	15	Japan	*kRas*	Sequence mutation	4.000	0.447–35.788	2
Kitago et al[33]	2004	20	Japan	*kRas*	Sequence mutation	1.364	0.112–16.577	3

First Author	Year	Total No. IPMNs	Study Area	Gene	Assay, Definition of Positivity	OR	95% CI	Study Quality (0–6)
Wada et al[34]	2004	23	Japan	*kRas*	Sequence mutation	3.063	0.472–19.879	2
Kobayashi et al[35]	2008	4	Japan	*kRas*	Sequence mutation	0.200	0.005–8.825	2
Schonleben et al[36]	2008	38	United States	*kRas*	Sequence mutation	1.429	0.270–7.549	2
Schonleben et al[37]	2007	same data as above	United States	*kRas*	Sequence mutation			2
Schonleben et al[38]	2008	same data as above	United States	*kRas*	Sequence mutation			1
Chadwick et al[39]	2009	52	United States	*kRas*	Sequence mutation	0.406	0.119–1.381	3
Fritz et al[40]	2009	20	United States	*kRas*	Sequence mutation	0.333	0.047–2.366	3
Jang et al[24]	2009	41	South Korea	*kRas*	Sequence mutation	5.867	1.395–24.673	4
Biankin et al[41]	2002	18	Australia	*p53*	>10% Cells positive by IHC	3.889	0.543–27.866	4
Jinfeng et al[42]	2002	22	Japan	*p53*	>10% Cells positive by IHC	25.000	1.168–535.241	2
Mueller et al[31]	2003	13	Germany	*p53*	PCR amplification and single-strand conformation polymorphism analysis of exons 5, 6, 7, 8	4.500	0.190–106.823	2
Sasaki et al[43]	2003	38	Japan	*p53*	>5% Cells positive by IHC	33.000	1.647–661.051	2
Uemura et al[32]	2003	15	Japan	*p53*	focal aggregates of >30 positive cells with nucleus stained brown	5.769	0.232–143.371	2
Wada et al[34]	2004	23	Japan	*p53*	Fluorescence-labeled microsatellite markers to detect loss of heterozygosity of 17p13	50.143	2.242–1121.352	1
Ito et al[21]	2005	21	Japan	*p53*	>5% Cells positive by IHC	3.250	0.340–31.074	5
Ueda et al[23]	2005	24	Japan	*p53*	A few positive cells, scattered staining, diffuse staining	11.118	0.508–243.105	1
Nishikawa et al[44]	2006	37	Japan	*p53*	>10% Cells positive by IHC	3.300	0.475–22.942	4
Abe et al[45]	2007	47	Japan	*p53*	>10% Cells positive by IHC	4.688	1.016–21.619	4
Miyasaka et al[46]	2007	128	Japan	*p53*	>10% Cells positive by IHC	25.000	3.153–198.205	4
Chadwick et al[39]	2009	52	United States	*p53*	>5% Cells positive by IHC	0.535	0.146–1.962	3
Jang et al[24]	2009	41	South Korea	*p53*	>10% Cells positive by IHC	8.767	0.458–167.937	3
Nodari et al[47]	2003	2	Italy	*Telomerase*	Reverse transcriptase–PCR	9.000	0.097–831.780	0
Hashimoto et al[48]	2008	12	Japan	*Telomerase*	IHC	39.667	1.279–1229.867	4
Hashimoto et al[49]	2008	68	Japan	*Telomerase*	IHC	9.750	2.676–35.528	5
Koshiba et al[50]	1999	26	Japan	*Cox2*	IHC	23.000	1.070–494.573	2
Kokawa et al[51]	2001	29	Japan	*Cox2*	>5% Cells positive by IHC	1.697	0.332–8.666	2
Aoki et al[52]	2002	30	Japan	*Cox2*	IHC	5.833	1.119–30.403	3
Niijima et al[53]	2002	32	Japan	*Cox2*	>10% Cells positive by IHC	1.244	0.262–5.915	3

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First Author	Year	Total No. IPMNs	Study Area	Gene	Assay, Definition of Positivity	OR	95% CI	Study Quality (0–6)
Jang et al[24]	2009	41	South Korea	*Cox2*	IHC	2.955	0.310–28.140	2
Jang et al[54]	2007	55	South Korea	*Shh*	IHC	6.691	1.946–23.000	3
Liu et al[55]	2007	18	Taiwan	*Shh*	IHC	10.455	0.425–256.957	0
Satoh et al[56]	2008	63	Japan	*Shh*	>20% Cells positive by IHC	5.940	0.322–109.490	4