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META-ANALYSIS

Role of Notch signaling pathway in gastric cancer: A meta-analysis of the literature

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Abstract

AIM: To perform a meta-analysis to quantitatively summarize the evidence for the association between the Notch signaling pathway and gastric cancer (GC).

METHODS: An electronic search of the MEDLINE, EMBASE and Chinese National Knowledge Infrastructure, which contain articles published from 1966 onwards, was conducted to select studies for this meta-analysis.

RESULTS: Fifteen studies with a total of 1547 gastric cancer cases and 450 controls were included in this meta-analysis. Overall, the expression of Notch1, Notch2, Delta-like 4 and Hes1 was significantly higher in tumor tissues of GC compared to normal tissues. Specifically, stratified analyses showed that significantly increased expression of Notch1 was associated with non-cardia location, > 5 cm size, diffuse type, positive lymphovascular invasion and distal metastasis. Statistically significant higher expression of Notch3 was found in diffuse type GC. Jagged1 was also significantly over-expressed in diffuse type and poor differentiation type of GC. DLL4 was significantly over-expressed in advanced T stage, N stage and TNM stage in GC patients. However, the stratified analysis showed that there was no statistically significant difference in Hes1 expression between different subgroups. Sporadic reports showed that Notch1 and Jagged1 were independent poor prognostic predictors in GC.

CONCLUSION: The Notch signaling pathway plays an important role in tumor progression of gastric cancer.

Key words: Notch; Gastric cancer; Incidence; Prognosis; Meta-analysis

Core tip: This article quantitatively summarizes the evidence for the association between Notch signaling pathway and gastric cancer (GC) by meta-analysis, and finds that Notch1 and Notch2 signaling pathways have been activated in GC; increased expression of Notch1 is associated with non-cardia location, > 5 cm size, diffuse type, positive lymphovascular invasion and distal metastasis; Notch1 and Jagged1 may be independent poor prognostic predictors in GC. Notch signaling may participate in tumor formation and progression of GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most fatal malignancies

and the fourth most common cancer worldwide, although its overall incidence is decreased in recent years[1]. 21600 new cases and 10990 new deaths of GC were estimated to occur in 2013 in United States[2] and these rates might double in Asian or Pacific Islanders due to the high rate of chronic infection with *Helicobacter pylori* (*H. pylori*). Some risk factors for this disease have been revealed, including diet, *H. pylori* infection and genetic alterations[3,4]. However, so far, less is known about how GC exactly occurs, although numerous investigations have been conducted.

The Notch signaling pathway plays a pivotal role in self-renewal of stem cells and cell-fate determination of progenitors[5]. In mammals, there are four Notch receptors (Notch 1-4) and five ligands, two of the Jagged family (Jagged1-2) and three of the Delta-like family (DLL1, DLL3, DLL4)[6]. After binding of the receptors to their ligands, the γ-secretase complex mediates the cleavage of the transmembrane domain of the Notch receptor to release the intracellular domain of the Notch receptor (NICD). Then, NICD translocates into the nucleus and works as a transcriptional coactivator, thus regulating the expression of target genes, including the hairy enhancer of split (Hes) and Hes-related (Hey) family[6].

Currently, a number of case-control studies have been conducted to investigate the association between the Notch signaling pathway and gastric cancer in humans. However, the function of components of the Notch pathway in GC is still controversial, because different even opposite effects were indicated. To date, no quantitative summary of the evidence has ever been performed. Therefore, we conduct this meta-analysis to quantitatively summarize the evidence for the roles which the Notch signaling pathway plays in GC.

MATERIALS AND METHODS

Literature search strategy

A search of the following electronic databases was performed: MEDLINE (1966 to December 2012), EMBASE (1980 to December 2012) and Chinese National Knowledge Infrastructure (CNKI) (1979 to December 2012). The following key words or text words were used: Notch or Notch intracellular domain or NICD or Delta or Delta-like or DLL or Jagged or HES or Herp or Hey, AND gastric or stomach or cardia or gastrointestinal, AND adenocarcinoma or carcinoma or cancer or neoplasm or tumor or tumour. Only studies conducted on human subjects were included, without restriction on language. The reference lists of reviews and retrieved articles were hand searched at the same time. We did not consider abstracts or unpublished reports. If more than one article was published by the same author using the same case series, we selected the study with higher sample size.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. For inclusion in the meta-analysis, the identified articles have to provide information on: (1) any study describing the association of at least one component of the Notch signaling pathway with gastric cancer; (2) any study reporting the numbers of both controls and gastric cancer cases; (3) results expressed as odds ratio (OR) with 95%CIs; and (4) case-control or nested case-control studies. Major reasons for exclusion of studies were (1) no control; (2) duplicate; or (3) no usable data reported.

Data extraction

All data were extracted independently by 2 investigators (Du X and Cheng Z) according to the pre-specified selection criteria. Disagreement was resolved by the investigator (Hu JK), who participated in the discussion with them and made an ultimate decision. The following data were extracted: study design and period, statistical methods, population, number of gastric cancer cases and controls studied and results of studies.

Statistical analysis

Statistical analyses were performed using Reviewer Manager Software (Version 5.1.7, The Nordic Cochrane Centre, Cochrane Collaboration), which was provided by Cochrane Collaboration. $P < 0.05$ was considered statistically significant. Meta-analysis was done using either the random effects model or fixed effects model. Heterogeneity was checked by the χ^2 test. If the results of the trials had heterogeneity, the random effects model was used for meta-analysis. The results were expressed as OR for the categorical variables and 95%CI. In addition, we observed whether there was any publication bias by use of the funnel plot, but tests for funnel plot asymmetry were only used when there are at least ten studies included in each meta-analysis.

RESULTS

Study characteristics

A total of 522 articles in English and 32 in Chinese were retrieved (Figure 1). After screening the title, reviewing the abstract and reading the full-text articles, 15 cohort studies were finally identified to match our inclusion criteria (shown in Supplementary data)[7-21]. Studies were carried out in China, Japan, South Korea and Italy. In those 15 studies which investigated the associations with gastric cancer regarding components of the Notch signaling pathway, 13 focused on acceptor Notch1[7-11,13-20], 4 on ligand Jagged1[9,16,17,20], 3 on target protein Hes1[9,13,14], and 2 on ligand DLL4[18,21]. Only 1 study focused on Notch2[13], Notch3[9], Jagged2[9] and DLL1[16], respectively. Characteristics of the studies included in this meta-analysis are presented in Table 1.

Quantitative data synthesis

Notch1: The combined results based on the included studies showed that there was a significant difference in Notch1 expression between GC tissue and normal tissue,

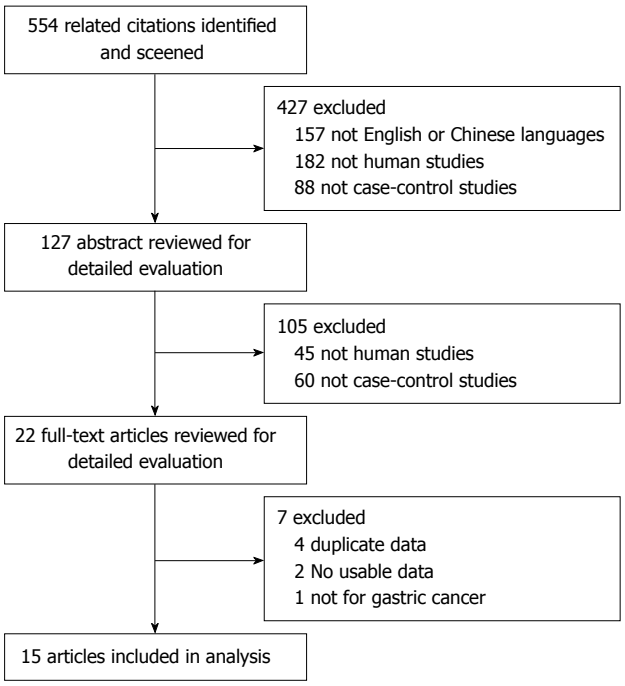

Figure 1 Flow diagram of study identification, inclusion, and exclusion.

and Notch1 expression was significantly higher in GC than in the control group (OR = 2.90, 95%CI: 2.07-4.07) (Figure 2A).

When stratifying for gender in GC, we found that there was not a statistically significant difference in Notch1 expression between males and females (OR = 1.21, 95%CI: 0.92-1.59) (Table 2). Similar results were also found in various stratified analyses of age (≤ 60 years *vs* > 60 years), histological differentiation (well/moderate *vs* poor/undifferentiated), T stage (T1-2 *vs* T3-4), N stage (N0 *vs* N1-3) and tumor node metastasis (TNM) stage (stages Ⅰ-Ⅱ *vs* Ⅲ-Ⅳ) (Table 2). When stratifying by the location, tumor size, Lauren's classification, lymphovascular invasion, and distal metastasis, we observed statistically significant differences in Notch1 expression between these subgroups (Table 2).

Statistically significant heterogeneity was observed among the included studies (χ^2 = 64.84, P < 0.00001, I^2 = 89%) (Figure 2A). Test of publication bias was shown by the funnel plot (Figure 2B). This is a scatter plot of the OR estimated from individual studies plotted on the horizontal axis (HOR), against the standard error of the estimate shown on the vertical axis (SE (log[OR])). Most of the studies analyzed lied within the 95% confidence interval (Figure 2B). Review of funnel plots could not rule out the potential for publication bias for the analysis.

Jagged1: The combined results based on all studies showed that there was no significant difference in Jagged1 expression between gastric cancer tissue and normal tissue (OR = 0.94, 95%CI: 0.00-254.96) (Figure 3A, Table 3). When stratifying for gender, age, location, T stage, N stage and TNM stage, no significant differences were among subgroups in patients with GC. When stratifying for Lauren's classification and histological differentiation, overall meta-analysis showed that Jagged1 expression was significantly different between intestinal type GC (i-GC) and diffuse type GC (d-GC) subgroups, well or moderate differentiation and poor or undifferentiated differentiation subgroups in GC patients (Table 3).

DLL4: The combined results based on all studies showed that the expression of DLL4 was significantly higher in cancer tissue of GC than in normal tissue (OR = 3.84, 95%CI: 2.52-5.83) (Figure 3B, Table 3). When stratifying for T stage, N stage and TNM stage, overall meta-analysis showed that DLL4 was significantly over-expressed in advanced stage in GC patients. There was no significant difference observed when stratifying for gender, age, differentiation and distal metastasis in patients with GC (Table 3).

Hes1: The combined results based on all studies showed that there was a significant difference in Hes1 expression between GC tissue and normal tissue (OR = 14.31, 95%CI: 4.11-49.87) (Figure 3C, Table 3). When stratifying for gender, age, Lauren's classification, histological differentiation, T stage, N stage, distal metastasis and TNM stage, we found no statistically significant difference between subgroups in patients with GC (Table 3).

Other components of Notch signaling pathway: There were significant differences between gastric cancer tissue and normal tissue in Notch2 expression (OR = 292.00, 95%CI: 23.75-3589.39) (Table 3). No difference in Notch2 expression was found between i-GC and d-GC, whereas Notch3 expression was significantly higher in i-GC compared to d-GC. Jagged2 expression was also significantly different among subgroups by Lauren's classification and T stage (Table 3).

Prognostic impact of Notch signaling pathway: A small number of articles reported the prognostic significance of the Notch signaling pathway in GC. Positive expression of Notch1 or Jagged1 protein has been proven to be associated with poor prognosis, respectively[10,15,17], and both were independent prognostic predictors in GC[10,17]. Kang *et al*[9] showed that high mRNA expression of Notch3 and Jagged2 was related to better survival outcome on univariate analysis, and only Notch3 expression was an independent marker of prognosis when using multivariate Cox's proportional hazard regression analysis.

DISCUSSION

Notch signaling is a key pathway in the self-renewal of stem cells, cell fate determination and differentiation during embryonic and postnatal development and adult cell homeostasis. So far, the role of each Notch component, as an oncogene or a tumor suppressor, is still controversial. Clearly, the function of Notch signaling is context-dependent and could act both as an oncogene

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Country	Ethnicity	Study design	Detected target	No. of cases detected for Notch1	No. of controls detected for Notch1	No. of cases detected for Hes1	No. of controls detected for Hes1	No. of cases detected for Jagged1	No. of controls detected for Jagged1
Gou *et al*[7]	China	Asians	HCC	Notch1	108	NC	-	-	-	-
Huang *et al*[8]	China	Asians	HCC	Notch1	68	28	-	-	-	-
Kang *et al*[9]	South Korea	Asians	HCC	Notch1, Notch3, Jagged1, Jagged2, Hes1	103	NC	103	NC	103	NC
Li *et al*[10]	China	Asians	HCC	Notch1	168	27	-	-	-	-
Liu *et al*[11]	China	Asians	HCC	Notch1	317	NC	-	-	-	-
Piazzi *et al*[12]	Italy	Caucasians	HCC	DLL1	-	-	-	-	-	-
Sun *et al*[13]	China	Asians	HCC	Notch1, Notch2, Hes1	74	10	74	10	-	-
Wang *et al*[14]	China	Asians	HCC	Notch1, Hes1, NICD	72	16	72	16	-	-
Yang *et al*[15]	China	Asians	HCC	Notch1	135	27	-	-	-	-
Yang *et al*[16]	China	Asians	HCC	Notch1, Jagged1, DLL1	63	63	-	-	63	63
Yeh *et al*[17]	Taiwan, China	Asians	HCC	Notch1, Jagged1	90	NC	-	-	96	NC
Zhang *et al*[18]	China	Asians	HCC	Notch1, DLL4	45	25	-	-	-	-
Zhang *et al*[19]	China	Asians	HCC	Notch1	54	54	-	-	-	-
Zhou *et al*[20]	China	Asians	HCC	Jagged1, Notch1	60	NC	-	-	60	20
Ishigami *et al*[21]	Japan	Asians	HCC	DLL4	-	-	-	-	-	-

HCC: Hospital-based case-control; NC: No control; DLL: Delta-like; NICD: Intracellular domain of Notch.

Table 2 Meta-analysis of Notch1 and gastric cancer

Stratification of gastric cancer	No. of participants	OR (95%CI)	Statistical method	*P* value	Ref.
Gender: Male *vs* female	1040	1.21 (0.92-1.59)	Fixed	0.18	9[8-11,15,17-20]
Age (yr): ≤ 60 *vs* > 60	607	1.36 (0.96-1.91)	Fixed	0.08	4[8,10,11,19]
Location: Cardia *vs* noncardia	589	0.62 (0.43-0.91)	Fixed	0.01[a]	5[8,11,17,19,20]
Tumor size: ≤ 5 cm *vs* > 5 cm	634	0.68 (0.49-0.94)	Fixed	0.02[a]	5[8,11,15,19,20]
Lauren's classification: Intestinal *vs* diffuse	680	1.45 (1.03-2.03)	Fixed	0.03[a]	5[9,11,13,15,17]
Histological differentiation: Well/moderate *vs* poor/undifferentiated	1220	1.42 (0.85-2.37)	Random	0.17	11[7-11,14,15,17-20]
Lymphovascular invasion: Negative *vs* positive	258	0.49 (0.28-0.87)	Fixed	0.01[a]	2[10,17]
T stage: T1-2 *vs* T3-4	453	0.71 (0.24-2.09)	Random	0.54	5[7,10,14,18,20]
N stage: N0 *vs* N1-3	1220	1.07 (0.57-2.00)	Random	0.83	11[7-11,14,15,17-20]
Distal metastasis: Negative *vs* positive	285	0.33 (0.14-0.78)	Fixed	0.01[a]	3[10,14,18]
TNM stage: Stages Ⅰ-Ⅱ *vs* Ⅲ-Ⅳ	567	0.91 (0.53-1.57)	Random	0.74	7[8,9,14,15,17-19]

[a]*P* < 0.05. TNM: Tumor node metastasis.

and as a tumor suppressor gene in tumorigenesis of different types of cancer[22,23]. For instance, Notch has an oncogenic role in colorectal cancer[24], breast cancer[25], lung cancer[26], and neuroblastoma[27]. On the contrary, Notch acts as a tumor suppressor in squamous cell carcinoma of the skin[28] and cervical uterus[29], hepatocellular carcinoma and neuroendocrine tumors of the lung and gastrointestinal tract[30]. The multifaceted features of Notch family members suggest the necessity to check the activation patterns and potential roles of Notch signaling in different tumor types without any initial impression. Researchers also focused on the relationship between the Notch signaling pathway and gastric cancer, and a rapidly growing number of related outcomes has

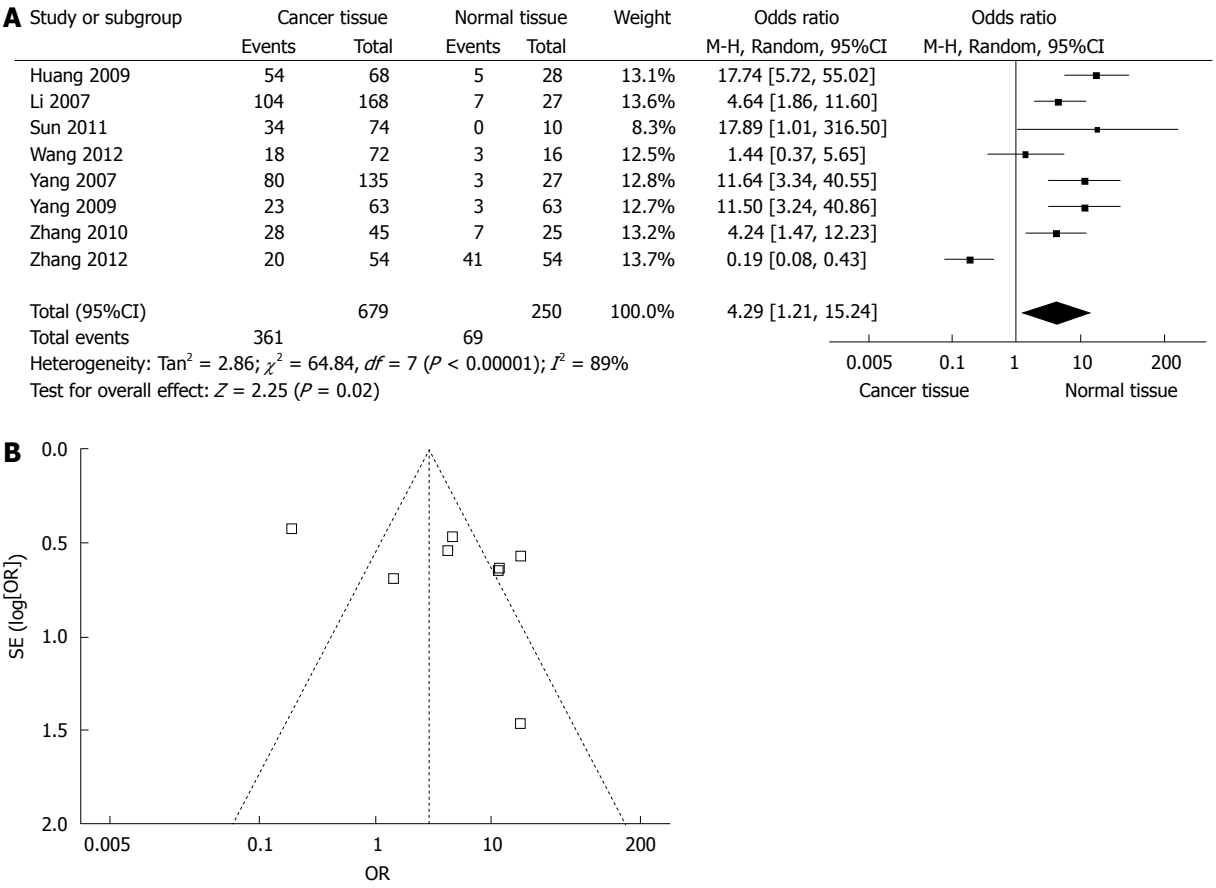

Figure 2 Forest plot for the association between Notch1 and gastric cancer (A) and funnel plot for all studies included in this meta-analysis of Notch1 and gastric cancer (B).

created but conclusions remain controversial[8,13,19]. For example, Zhang *et al*[19] found that Notch1 expression was decreased in gastric tumors compared to normal tissue, which was contrary to the traditional concept. Meta-analysis provides a quantitative approach for combining the results of various studies on the same topic, and for estimating and explaining their diversity.

In this meta-analysis, we searched all English and Chinese articles focused on the role of Notch signaling in GC. Surprisingly, only 1 paper was conducted in Caucasians, and others were all investigated in Asian countries. Geographical distribution imbalance of GC due to the diverse infection rate of *H. pylori* may be one of major reasons. Notch1 has been found to be expressed in most GC cell lines as well as normal gastric mucosa[31], but other data showed that no expression was detected in normal gastric mucosa[13]. According to the results of the current study, we found that Notch1 was expressed in both gastric cancer tissues and normal mucosa, but significantly higher expression was seen in cancer tissues than in normal tissues (OR = 2.90, $P = 0.02$), suggesting that Notch1 is activated in GC. This is consistent with the role of Notch1 as an oncogene in many solid malignancies. Thus far, mutated Notch1 has only been detected in T-cell acute lymphoblastic leukemia, but not in other common human cancers including GC[32]. More interestingly, Notch1 was found to be more preferably expressed in intestinal metaplasia tissues and well-differentiated intestinal type GC (i-GC), whereas four poorly or undifferentiated GC cell lines were negative for its expression. Our meta-analysis also found that higher Notch1 expression was seen in i-GC, but no differences existed in relation to histological differentiation. Therefore, it is speculated that Notch1 itself, not mutated type, may play a role in promoting metaplastic transition of gastric epithelial cells to tumor cells. Moreover, GC patients with larger tumor size (> 5 cm), positive lymphovascular invasion and distal metastasis had significantly higher expression rates of Notch1 (Table 2), suggesting that Notch1 may also participate in tumor progression and metastasis of GC.

Only one study considering Notch2 function was included in this review. Notch2 has also been proven to act as an oncogene in some types of cancers, and in GC, Notch2 expression was rare in normal or inflammatory tissues, whereas in both i-GC and d-GC tissues the positive rate could reach as high as 98.6% and 97.3%, respectively[13]. Although some authors found that inhibition of the Notch2 pathway with γ-secretase antagonists may not cause either growth arrest or death of GC cells, this phenomenon may be a result of other signaling pathways' compensation in response to the suppressed Notch signaling activity[13]. Conversely, other studies showed that activation of Notch2 signaling would promote both cell proliferation and xenografted tumor

Table 3 Meta-analysis of other components of Notch signaling pathway and gastric cancer

Stratification of gastric cancer	Notch2		Notch3		Jagged1		Jagged2		DLL4		Hes1	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Tumor tissue *vs* normal tissue	292.00 (23.75-3589.39)	< 0.01[a]	-	-	0.94 (0.00-254.96)	0.98	-	-	3.84 (2.52-5.83)	< 0.01[a]	14.31 (4.11-49.87)	< 0.01[a]
Gender: Male *vs* female	-	-	1.01 (0.46-2.26)	0.97	1.26 (0.36-4.39)	0.36	2.90 (0.76-11.02)	0.12	1.03 (0.57-1.86)	0.93	1.05 (0.47-2.35)	0.90
Age (yr): ≤ 55 *vs* > 55	-	-	0.75 (0.30-1.88)	0.54	1.19 (0.48-2.94)	0.70	0.17 (0.02-1.40)	0.10	0.52 (0.13-2.16)	0.37	1.13 (0.45-2.81)	0.80
Location: Cardia *vs* noncardia	-	-	-	-	0.63 (0.26-1.50)	0.30	-	-	-	-	-	-
Lauren's classification: Intestinal *vs* diffuse	0.60 (0.02-15.19)	0.76	2.61 (1.17-5.84)	0.02[a]	2.02 (1.11-3.69)	0.02[a]	3.97 (1.17-13.46)	0.03[a]	-	-	1.71 (0.88-3.30)	0.11
Histological differentiation: Well/moderate *vs* poor/undifferentiated	-	-	2.04 (0.89-4.67)	0.09	2.18 (1.23-3.86)	< 0.0[a]	1.36 (0.44-4.18)	0.60	0.89 (0.52-1.54)	0.69	1.78 (0.95-3.34)	0.07
T stage: T1-2 *vs* T3-4	-	-	2.40 (0.73-7.92)	0.15	0.50 (0.03-8.54)	0.63	3.70 (1.05-13.08)	0.04[a] (T1 *vs* T2-4)	0.29 (0.16-0.54)	< 0.01[a]	1.72 (0.49-6.00)	0.39 (T1 *vs* T2-4)
N stage: N0 *vs* N1-3	-	-	1.84 (0.71-4.75)	0.21	0.82 (0.44-1.50)	0.51	0.91 (0.23- 3.55)	0.89	0.12 (0.06-0.23)	< 0.01[a]	0.39 (0.04-4.38)	0.45
Distal metastasis: Negative *vs* positive	-	-	-	-	-	-	-	-	0.55 (0.10-3.00)	0.49	1.76 (0.36-8.51)	0.48
TNM stage: Stages Ⅰ-Ⅱ *vs* Ⅲ-Ⅳ	-	-	1.19 (0.54-2.63)	0.67	0.78 (0.42-1.42)	0.41	1.32 (0.44-3.98)	0.62	0.15 (0.03-0.80)	0.03[a]	0.70 (0.15-3.36)	0.66

[a]$P < 0.05$. DLL: Delta-like; TNM: Tumor node metastasis.

growth of GC cells[33]. More importantly, co-expression and nuclear co-translocation of Notch2 and target protein Hes1 were found to be more frequent than Notch1 both *in vivo* and *in vitro* in GC[13], suggesting that Notch2 mediated signaling would be more important in GC carcinogenesis and progression.

Using qRT-PCR tests, Notch3, Jagged1 and Jagged2 expression were found to be increased significantly in tumors compared to normal tissue[9]. Our meta-analysis results showed that overexpression of Notch3, Jagged1 and Jagged2 was associated with intestinal-type carcinomas ($P < 0.05$, Table 3). Moreover, Jagged1 expression has been correlated with aggressiveness of GC and poor survival rate[34]. Jagged2 was also found to be expressed significantly higher in early T stage, implying a possibility that Jagged2 may participate in the initiation of tumorigenesis. Other two Notch ligands DLL1 and DLL4 have been found to be able to control Notch1 signaling activation in GC[35], and expression of DLL4 was associated with advanced T and TNM stages. However, the exact roles of Notch3, Jagged and DLL in gastric carcinogenesis remain unclear.

Hes family members are major downstream target genes in the network of Notch signaling pathway, thus, high expression of Hes partially reflects activation of Notch signaling. Hes1/4/6 were expressed in most GC cell lines as well as normal gastric mucosa, while Hes2/3 were expressed in neither these cell lines nor the normal stomach[31,36]. From our meta-analysis, Hes1 expression was significantly higher in tumor tissues than in normal tissues (OR = 14.31, $P < 0.01$). Further investigation found that Hes1 could repress transcription of the ATOH1 gene, which encodes a transcription factor implicated in the gastrointestinal epithelial differentiation. These facts indicate that the canonical Notch signaling pathway might play a role in maintenance of stem or progenitor cells through inhibition of epithelial cell differentiation in gastrocarcinogenesis[37].

Few studies focused on the prognositic significance of Notch signaling in GC was found, therefore we could not perform a collective meta-analysis. Sporadic reports showed that positive expression of Notch1 and Jagged1 was independent makers for poorer prognosis. This is consistent with our meta-analysis results that Notch1 and Jagged1 were more frequently expressed in advanced GC. Kang *et al*[9] showed that high mRNA expression of Notch3 and Jagged2 was associated with prolonged survival, whereas our meta-analysis failed to show significant clinicopathological value of Notch3 and Jagged2. The real mechanism of these components acted in GC needs to be further investigated.

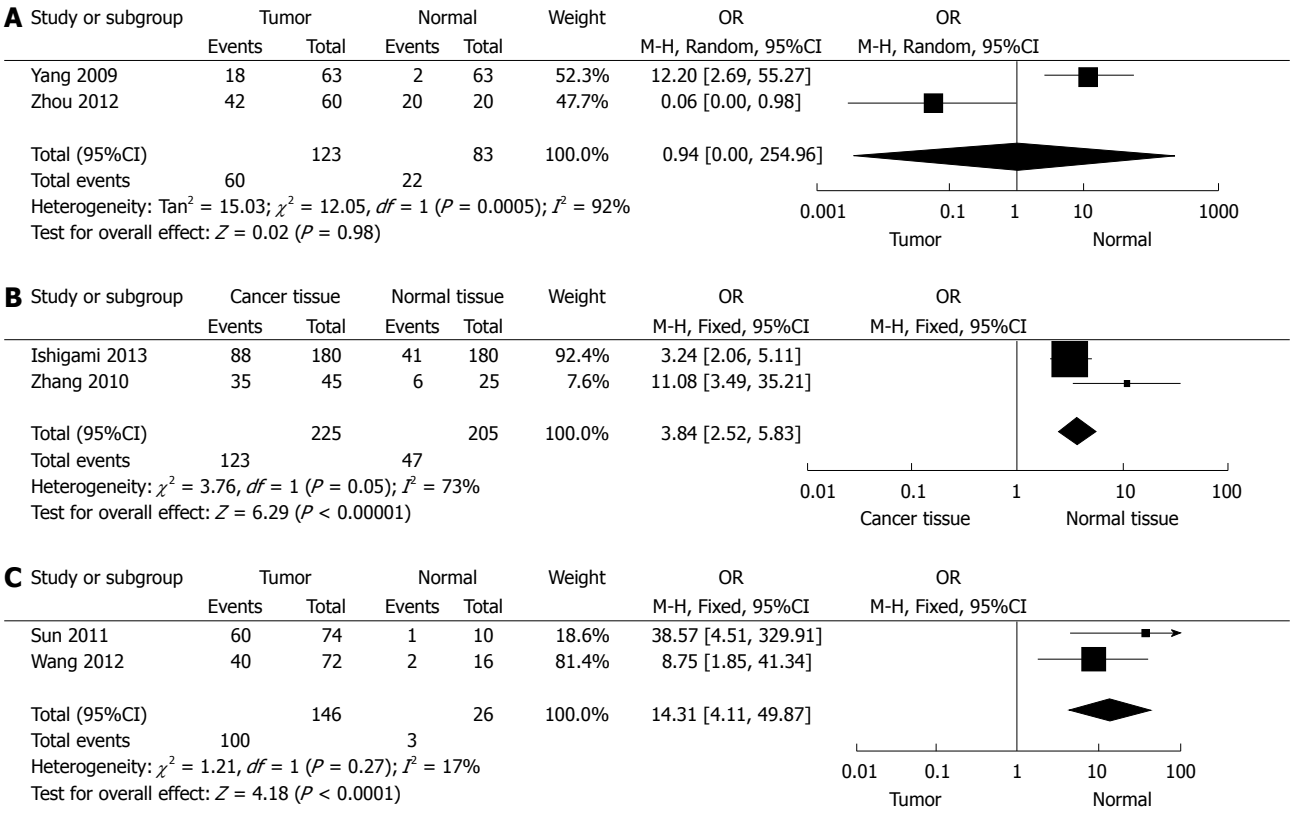

Figure 3 Forest plot. A: For the association between Jagged1 and gastric cancer; B: For the association between Delta-like 4 and gastric cancer; C: For the association between Hes1 and gastric cancer.

There are several limitations in this meta-analysis. First, only published studies were included in the meta-analysis; therefore, publication bias may have occurred as shown in Figure 2B. Second, as in most meta-analyses, these results should be interpreted with caution because the populations were from different countries and controls were not uniform. Third, no information on the association between infection with *H. pylori*, a strong risk factor for GC, and Notch signaling was obtained from most studies. Fourth, the conclusions drawn from subgroup analyses may be limited because of the small sample size. To minimize the potential bias, we designed a rigorous protocol before conducting meta-analysis, and performed a scrupulous search for published studies using explicit methods for study selection, data extraction and statistical analysis.

In summary, this meta-analysis suggests that Notch1 and Notch2 signaling pathways have been activated in gastric cancer and Notch signaling may participate in tumor formation and progression. Better designed studies based on larger cases both *in vivo* and *in vitro* are needed to further evaluate the role that the Notch signaling pathway plays in gastric carcinogenesis.

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COMMENTS

Background

The role of the Notch signaling pathway in gastric cancer has been widely researched; however, the real relationship remained unclear, and studies investigating the association between Notch signaling pathway and gastric cancer still reported conflicting results.

Research frontiers

The Notch signaling pathway plays a pivotal role in self-renewal of stem cells and cell-fate determination of progenitors, and its function is context-dependent and could act both as an oncogene and as a tumor suppressor gene in tumorigenesis of different types of cancer. The objective of this systematic review is to quantitatively summarize the evidence for the relationship between the Notch pathway and gastric cancer.

Innovations and breakthroughs

This article quantitatively summarizes the evidence for the association between the Notch signaling pathway and gastric cancer by meta-analysis, and finds that Notch1 and Notch2 signaling pathways have been activated in gastric cancer; increased expression of Notch1 is associated with non-cardia location, > 5 cm size, diffuse type, positive lymphovascular invasion and distal metastasis; Notch1 and Jagged1 may be independent poor prognostic predictors in gastric cancer.

Applications

Notch signaling may participate in tumor formation and progression of gastric cancer.

Peer review

This is a good descriptive paper that provides cutting edge information on the Notch signaling pathway in gastric cancer, which will provide great interest to readers. It is a rigorous and thorough report which clearly states and adds important information.

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