



c-erbB-2 expression and prognosis of gastric cancer: a meta-analysis

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ABSTRACT. The prognostic role of c-erbB-2 in gastric cancer is controversial. We conducted a meta-analysis to evaluate the relationship between c-erbB-2 expression and the prognosis of gastric cancer. We evaluated 20 published studies assessing the relationship between c-erbB-2 and gastric cancer prognosis. The Revman 5.0 software was used to perform literature retrieval, article selection, data collection, and statistical analysis. We utilized a fixed-effect model to pool hazard ratios and 95% confidence intervals from the studies. A total of 20 eligible studies including 4468 gastric cancer patients were analyzed. We were unable to demonstrate the prognostic value of c-erbB-2 for gastric cancer (hazard ratio = 1.01, 95% confidence interval = 0.87-1.16, P = 0.93). The present study indicated that c-erbB-2 expression is not a prognostic factor for gastric cancer.

Key words: c-erbB-2; Gastric cancer; Meta-analysis; Prognosis

INTRODUCTION

Gastric cancer has become one of the most common causes of cancer-related deaths in recent years (El-Rifai and Powell, 2002). In China, there are approximately 160,000 deaths from gastric cancer each year (Chen et al., 2004). The most frequently studied molecular biological prognostic factor in gastric cancer is c-erbB-2 (p185, HER-2/neu) (Jain et al., 1991; Yonemura et al., 1991; Sasano et al., 1993; Li, 1994; Gong et al., 1996; Pauletti et al., 1996; Lin and Zhu, 1998; Nakajima et al., 1999; Allgayer et al., 2000; Shao et al., 2000; Kubicka et al., 2002; Pinto-de-Sousa et al., 2002; García et al., 2003; Lee et al., 2003; Park et al., 2006; Gravalos and Jimeno, 2008; Barros-Silva et al., 2009; Yu et al., 2009; Grabsch et al., 2010; Zhou et al., 2013). However, the association between c-erbB-2 and gastric cancer prognosis remains unclear.

c-erbB-2 is a 185-kDa transmembrane tyrosine kinase receptor and a member of the epidermal growth factor receptor family, binds different ligands to the extracellular domain, and initiates a signal transduction cascade that can influence various aspects of tumor cell biology, including cell proliferation, apoptosis, adhesion, migration, and differentiation (Gravalos and Jimeno, 2008). Previous studies have indicated that overexpression of c-erbB-2 affects gastric cancer prognosis (Yonemura et al., 1991; Sasano et al., 1993; Pauletti et al., 1996; Shao et al., 2000; Pinto-de-Sousa et al., 2002; Yu et al., 2009; Zhou et al., 2013). However, the prognostic value of c-erbB-2 in patients with gastric cancer remains controversial. The aim of this study was to more precisely estimate the prognostic value of c-erbB-2 overexpression in gastric cancer.

MATERIAL AND METHODS

Publication search

We searched the PubMed, Embase, American Association for Cancer Research (AACR), Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), and Wanfang databases using the search terms “c-erbB-2” or “p185” or “HER-2/neu” and “gastric cancer” or “gastric carcinoma” and “prognosis” updated until January 2014. We manually searched through the reference lists of all identified articles and reviews for additional potentially eligible original reports.

Inclusion criteria

The inclusion criteria were as follows: 1) clinical research directly examining c-erbB-2 expression in gastric cancer, without any restriction on language or publication year; 2) the research subjects were gastric cancer patients without any restrictions on age or race; and 3) outcome indicators included overall survival.

Exclusion criteria

The major exclusion criteria were as follows: 1) duplicate data; 2) case reports, series, abstract, comment, review, and editorial; and 3) insufficient data.

Literature quality assessment and data extraction

We collected the following information: author, year of publication, country of origin, ethnicity, number of cases, and c-erbB-2 detection method. In a few studies, some of the data had already been reported elsewhere; therefore, only the novel data were included.

Data analysis

Meta-analyses were performed using the RevMan 5.0 software. We used the Q-test and the I^2 test to examine heterogeneity between studies. We used the hazard ratio (HR) value to evaluate the relationship between c-erbB-2 expression and overall survival in gastric cancer. To test publication bias, we utilized the RevMan 5.0 statistical software to construct a funnel plot. $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Literature screening

A total of 346 studies were initially identified, and 326 were excluded because of duplicate publication, insufficient data, or because they were nonclinical-based studies. A total of 20 studies were included, all of which were clinical studies; 4468 patients were included in this analysis. c-erbB-2 overexpression was examined through tumor specimens and postoperative follow-up time was no less than 5 years (Table 1). Five studies prospectively collected patient data. Methods to determine c-erbB-2 status included immunohistochemistry with 3 studies additionally performing fluorescence *in situ* hybridization or Southern blot analysis. One of the studies using fluorescence *in situ* hybridization only included survival data of patients; the other 19 studies all abstracted the data from immunohistochemistry experiments.

Table 1. Characteristics of the included studies.

Author, year	Country	Methods	Case number
Yonemura et al., 1991	Japan	IHC	197
Hilton and West, 1992	England	IHC	87
Jain et al., 1991	England	IHC	68
Sasano et al., 1993	Japan	IHC	35
Li, 1994	China	IHC	73
Gong et al., 1996	China	IHC	97
Nakajima et al., 1999	Germany	IHC	128
Lin and Zhu, 1998	Portugal	IHC	106
Shao et al., 2000	Germany	IHC	149
Allgayer et al., 2000	Korea	IHC	189
Pinto-de-Sousa et al., 2002	Portugal	IHC	157
Kubicka et al., 2002	Germany	IHC	42
Lee et al., 2003	Korea	IHC/South	841
García et al., 2003	Spain	IHC	63
Im et al., 2005	Korea	IHC/FISH	94
Park et al., 2006	Korea	IHC/FISH	182
Barros-Silva et al., 2009	Portugal	IHC	256
Yu et al., 2009	China	IHC	669
Grabsch et al., 2010	Eng/Ger	IHC	909
Xu et al., 2013	China	FISH	126

c-erbB-2 expression and prognosis for gastric cancer

As shown in Figure 1, of these 20 studies, 15 included HR values and their 95% confidence intervals (CIs), which were directly used to evaluate c-erbB-2 expression and the prognosis of gastric cancer. Of the other 5 studies, the HR values and their 95% CIs were calculated using the provided data. We found no prognostic value of c-erbB-2 for gastric cancer (HR = 1.01, 95%CI = 0.87-1.16, P = 0.93).

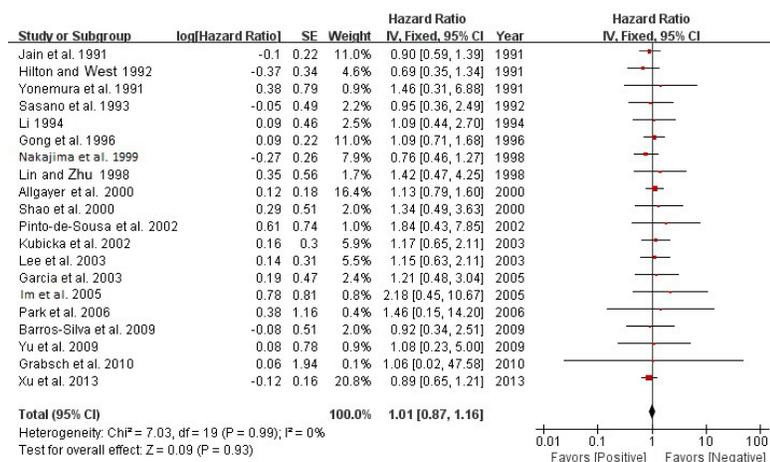


Figure 1. Forest plot of association between prognosis of gastric cancer and c-erbB-2 expression. The horizontal lines correspond to the study-specific HR and 95%CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of HR and 95%CI. In this analysis, the fixed-effect model was used.

Publication bias analysis

We analyzed publication bias using the Revman 5.0 software. The funnel plot (Figure 2) shows that the points were evenly distributed, symmetrical, and most were within the 95%CI. This indicates that no publication bias exists and that the results of our study are credible.

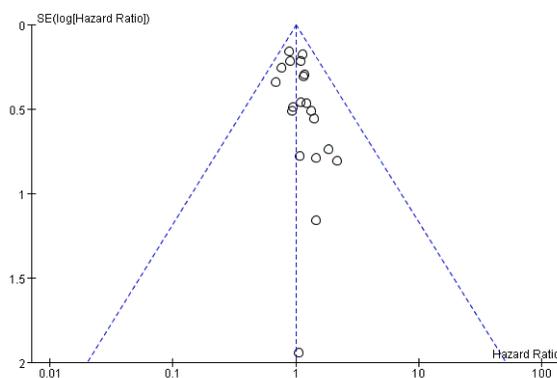


Figure 2. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log HR represents the natural logarithm of HR. The vertical line represents the mean effect size.

DISCUSSION

In the present meta-analysis, we did not find that c-erbB-2 was associated with the prognosis of gastric cancer. The prognosis of gastric cancer is related to the synergistic effects of several factors. For gastric cancer after curative surgery, prognosis factors such as age of patient, tumor location, tumor size, tumor differentiation degree, TNM stage, etc., are commonly used; among these factors, the TNM system (7th UICC) is accepted as a gold standard to evaluate gastric cancer prognosis. The 20 studies evaluated here incorporated clear diagnostic, inclusion, and exclusion criteria. The patients were grouped according to whether c-erbB-2 was expressed, with overall survival as the main outcome. The HR value was a statistical indicator used to assess the impact of different levels of c-erbB-2 on overall survival of patients with gastric cancer. In addition, several confounders, such as TNM-stage, age of patient, and *modus operandi*, may influence the prognosis of gastric cancer. If subgroup analysis was carried out using these confounding factors, a more accurate pooled HR may be calculated to clarify the relationship between c-erbB-2 expression and gastric cancer; however, because of the limitations of meta-analysis in evaluating observational studies, such as difficulties in obtaining primary materials or data, eliminating related confounding factors may overestimate the influence of c-erbB-2 expression on gastric cancer prognosis. Thus, our conclusion must be verified by prospective studies with larger sample sizes and multifactor analysis.

In summary, this meta-analysis of 20 studies showed that c-erbB-2 is not a significant prognostic factor in patients with gastric cancer.

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