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Review

Prognostic role of cyclooxygenase-2 in epithelial ovarian cancer: A meta-analysis of observational studies

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HIGHLIGHTS

- We performed a meta-analysis to evaluate the prognostic role of cyclooxygenase-2 (COX-2) in patients with ovarian cancer.
- This study showed that higher COX-2 expression was significantly associated with poor overall survival.
- Among studies which controls for covariates, a more prominent association was found between COX-2 expression and poor overall survival.

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ABSTRACT

Objective. The aim of this study was to evaluate the prognostic significance of cyclooxygenase-2 (COX-2) on survival in patients with ovarian cancer by using a meta-analysis of observational studies.

Methods. We searched Pubmed and Embase to retrieve observational studies evaluating the association between COX-2 status and survival in patients with ovarian cancer. Hazards ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were pooled across studies using a random-effects model.

Results. A total of 17 studies were included in this meta-analysis to estimate the association between COX-2 and overall survival (OS), disease-free survival (DFS), response to chemotherapy (RC), and other clinical parameters. In a random-effects meta-analysis of 15 studies, higher COX-2 expression significantly predicted poor OS (death HR, 1.34; 95% CI, 1.05–1.71; $I^2 = 56.5\%$). A more prominent association was found between COX-2 expression and poor OS when studies with adjustment for age, stage, and histology were included (death HR, 1.65; 95% CI, 1.25–2.17; $I^2 = 0\%$). However, higher COX-2 expression was not significantly associated with poor DFS (recurrence HR, 1.36; 95% CI, 0.79–2.33; $I^2 = 53.6\%$) and RC (OR, 1.89; 95% CI, 0.85–4.21; $I^2 = 17.6\%$). There was a marginally significant association between COX-2 positivity and several clinical parameters such as age, stage, and histology. The pooled ORs of higher COX-2 expression were 1.75 (95% CI, 1.01–3.04) for advanced stages, 1.34 (95% CI, 0.97–1.85) for old age, and 1.42 (95% CI, 0.98–2.05) for serous cancer in histologic type, respectively.

Conclusions. The present meta-analysis suggests that higher COX-2 expression may be an independent risk factor for poor OS in patients with ovarian cancer.

Contents

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Introduction

Epithelial ovarian cancer is the leading cause of death among female reproductive system diseases. The 5-year survival rate is 46%, and this low survival rate is attributable to the fact that about two-thirds of patients are diagnosed in an advanced stage [1]. It is necessary to identify prognostic factors to predict the outcomes of patients, which could be effective in making strategies and improving survival for ovarian cancer. Patient age, tumor histology, performance status, and residual tumor volume are considered as independent prognostic factors for survival in the late stage [2]. However, these factors are insufficient to predict the outcomes for the individual patient. Identifying molecular biological prognostic factors could enable to predict patients' outcomes more accurately and provide novel therapeutic targets.

Cyclooxygenases (COX) are key enzymes that are necessary for converting arachidonic acid into prostaglandin. Two isoforms of this enzyme, i.e., COX-1 and COX-2 have been identified. COX-1 is constitutively expressed, whereas COX-2 is an inducible enzyme activated by cytokines, growth factors, mitogen, and hormones [3]. Overexpression of COX-2 has been reported in epithelial ovarian cancer, and its overexpression rate is usually higher in invasive carcinomas than in borderline malignancies [4–7]. These support that COX-2 might be involved in critical steps of tumorigenesis. However, the prognostic role of COX-2 in ovarian cancer remains inconclusive.

In the current study, we performed a systematic review and meta-analysis of observational studies in order to evaluate the prognostic value of COX-2 for survival in patients with epithelial ovarian cancer.

Methods

Data search

We identified observational studies that evaluated the prognostic significance of COX-2 in ovarian cancer by performing a literature search of reports in PubMed and Embase from their respective inceptions until October 2012. Our overall search strategies included terms for COX-2 (COX-2, COX2, and cyclooxygenase-2) and ovarian cancer (ovarian cancer, ovarian neoplasm, ovarian tumor, and ovarian carcinoma).

Study selection

We independently screened the eligibility of all studies retrieved from the databases based on the predetermined selection criteria. We included observational studies in the analysis if a study reported or included the following: (1) COX-2 expression measured in epithelial ovarian cancer; (2) endpoints such as overall survival (OS), disease free survival (DFS), and response to chemotherapy (RC); (3) a hazard ratio (HR) and 95% confidence intervals (CIs) (or data to calculate them); and (4) histologically proven epithelial ovarian cancer. Studies published in languages other than English and animal studies were excluded. If the study population was duplicated in more than one study, either a study using more factors for adjustment or a study with the larger sample size was included.

Data extraction

We extracted the following data from each publication: first author, year of publication, country, study population, inclusion period, follow-up period, FIGO stage, assay method for COX-2 detection, high COX-2 cut-off level, prevalence of high COX-2 expression, results of survival analysis, HR with 95% CI, and methods of HR estimation.

Statistical analysis

The main outcomes were OS and DFS, comparing ovarian cancer patients with high expression of COX-2 to those with its low expression. For pooling estimates of survival results, we combined an HR and its 95% CI in each study. If the study reported both univariate and multivariate results, the latter one was used in the analysis. If these statistical variables were not available in an article, we estimated from given data using methods reported by Tierney et al. [8]. A survival curve could be read by Plot Digitizer (version 2.5.1) which is downloaded from http://autotrace.source.forge.net. Other outcomes were RC and other clinical parameters such as patient age, stage, histology, and tumor grade. For quantitative aggregation of such results, we collected ORs and their 95% CIs. A pooled HR or OR with its 95% CI was calculated by using a random-effects model (DerSimonian and Laird method) [9]. We examined heterogeneity in results across studies by using the Higgins I^2 value, which measures the percentage of total variance in the summary estimate due to between-study heterogeneity. An I^2 value more than 50% is recognized as significant heterogeneity [10,11]. For OS, subgroup analysis was conducted by the presence of adjustment variables, follow-up period, and study regions. To examine the potential publication bias, results were analyzed using the Egger's test and the Begg's funnel plot test [12,13]. All of the statistical analyses were performed by STATA 11.0 (StataCorp, College Station, TX).

Results

Study selection and characteristics

The process of identifying eligible studies is shown in Fig. 1. We identified 417 studies from Pubmed and Embase. A total of 305 studies remained after excluding duplicate articles. Titles and abstracts of all identified studies were reviewed to exclude those that were clearly irrelevant. A total of 60 potentially relevant articles were fully reviewed with the full text. Among them, 43 articles were excluded because of the following reasons: 21 studies are not relevant; 8 studies are not original articles; 3 studies had insufficient data; 1 study involved non-epithelial ovarian cancer, and 10 studies had a duplicated study population. Finally, 17 studies were selected for our meta-analysis [4,5,14–28]. The main characteristics of the 17 eligible publications were shown in Table 1. Overall, OS was obtained from 15 articles. Among these studies, 9 studies measured HRs from multivariate analysis, while 6 studies obtained HRs from univariate analysis. Out of 15 studies, 7 studies reported HRs and 95% CIs. Because 8 studies did not provide HRs and 95% CIs, those were calculated from the data available in each study.