Abnormal COX2 Protein Expression May Be Correlated with Poor Prognosis in Oral Cancer: A Meta-Analysis

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1. Introduction

Oral cancer or mouth cancer is any cancerous tissue growth located in the oral cavity, which was regarded as the sixth most common diagnosed malignancy of all cancers worldwide [1]. Generally, over 90% of oral malignancies in the upper aerodigestive tract are squamous cell carcinomas, with the signs and symptoms of skin lesion, lump, ulcer, swallowing difficulty, and mouth sores [2]. As an important ongoing public health problem, the prevalence and morbidity of oral cancer were increased, with the number of an estimated 263,900 new invasive cases and 128,000 deaths in 2008 all over the world [3]. Furthermore, the majority of oral cancer patients had a significantly poor prognosis and the overall 5-year survival rate of oral cancer patients is less than 50% [3]. Indeed, oral cancer is known to be a complex and multifactorial disease which may be induced by the interaction of genetic and environmental factors [4, 5]. In the past few decades, tobacco use (both smoking and chewing) and alcohol consumption were considered to be the main risk factors for oral cancer, while age, gender, HPV infections, betel quid chewing, and other unhealthy lifestyles may also contribute to the pathogenesis and development of oral cancer [6, 7]. Recently, epidemiological study has revealed that cyclooxygenase-2 (COX-2) protein expression may be a biomarker for predicting the prognosis of oral cancer [8].

The cyclooxygenase 2 (COX2), also known as prostaglandin-endoperoxide synthase 2 (PTGS2) in humans, is one of the two isoforms of COX that is the rate-limiting enzyme in the metabolic conversion of arachidonic acid to prostaglandins, including prostaglandin E2, a major mediator of inflammation and angiogenesis [9, 10]. Although its physiological role is not fully known, COX2 may function
significantly in the inhibition of apoptosis and immune surveillance, the promotion of angiogenesis, the elevation of cancer invasiveness and metastasis, and the modulation of cell differentiation [11]. More importantly, COX2 is usually unexpressed under the normal circumstance in most cells, whereas increased levels are always found in response to inflammation reactions, growth factors, and tumor promoters [12]. In recent decades, overexpression of COX2 has been reported in various cancer types, such as those arising in the esophageal, breast, lung, colon, stomach, prostate, and urinary bladder [13–16]. On the contrary, selective COX2 inhibitors suppress growth of cells by inducing G0/G1, cell-cycle arrest, and cellular proliferation; thus apoptosis could have a reversed effect on the development and progression of cancers [17]. Similar to the results of the present study on the expression of COX2 and the pathogenesis of human tumors, previous reports have suggested a correlation between the expression of COX2 and the occurrence of oral cancer [18, 19]. In general, COX2 may initially stimulate angiogenesis and vascular endothelial cell growth that are essential in tumor growth and spread, promoting the production of prostaglandin E2 and cyclin-dependent kinase inhibitor P21 expression [20]. Due to its previous multiple functions, COX2 may participate in initiation, progression, invasion, and metastasis of cancer cells which are potential with clear prognostic implications and consequently contribute to the deterioration of human cancers [9]. In view of these above reasons, it was plausible to speculate that manipulation of serum levels of COX2 may be useful in the prediction of prognosis of oral cancer. In this regard, it may also be useful for the adoption of selective COX2 receptor-blocking agents in prevention of oral cancer by blocking initiation, progression, or metastasis of tumors [20]. In recent decades, several previous studies have confirmed that the elevated COX2 levels may be an indicator of biologically aggressive tumor prognosis based on its important role in tumor cells growth and metastasis [21, 22]; meanwhile other studies have also illustrated inconsistent results [8, 23]. Given the conflicting evidence on this issue, we conducted a meta-analysis of all available cohort studies to explore the associations between the serum level of COX2 and the prognosis in oral cancer patients.

2. Materials and Methods

2.1. Literature Search. Web of Science (1945–2013), the Cochrane Library Database (Issue 12, 2013), PubMed (1966–2013), EMBASE (1980–2013), CINAHL (1982–2013), and the Chinese Biomedical Database (CBM) (1982–2013) were searched for relevant articles without any language restrictions. The keywords and MeSH terms we used in conjunction with a highly sensitive search strategy were as follows: ["Cyclooxygenase 2" or "Cyclooxygenase 2 Inhibitors" or "cyclooxygenase 2" or "cyclooxygenase 2 inhibitors" or "Cyclo-Oxygenase II" or "PTGS2" or "PTGS-2" or "Prostaglandin H Synthase-2" or "Cyclooxygenase-2" or "prostaglandin synthase 2" or "COX2 Inhibitors" or "cyclooxygenase-2 Inhibitors"] and ["Mouth Neoplasms" or "oral neoplasm" or "oral cancer" or "mouth cancer" or "cancer of the mouth" or "oral carcinoma" or "mouth carcinoma" or "oral squamous cell carcinoma" or "OSCC"]). The above references of articles and reviews identified in the included articles were also performed to search for additional studies.

2.2. Inclusion and Exclusion Criteria. We collected all eligible articles about the relationship between COX2 and oral cancer in this meta-analysis. The study included in our meta-analysis should meet the following inclusion criteria: (1) COX2 expression is evaluated in the oral cancer tissues; (2) relationship is demonstrated between COX2 expression and oral cancer prognosis; (3) all data are collected by immunohistochemistry, and sufficient information about COX2 expression levels should be provided in the paper; (4) only the most complete single study was selected, if multiple studies investigated the same patients or potential overlapping patients. The exclusion criteria were also as follows: (1) letters, case reports, reviews, editorials, conference abstracts, and some non-English language articles; (2) papers that had no information of overall survival (OS) or that could not calculate the hazard ratios (HRs) about OS from the given information which were excluded.

2.3. Data Extraction and Methodological Assessment. Using a standardized form, data extraction was performed independently by two authors from each included study. Two investigators reviewed all of the articles that met the previous inclusion and exclusion criteria. Language of publication, publication year of article, the first author’s surname, geographical location, design of study, total number of cases, sample size, the source of the subjects, detection method of protein expression, expression levels, TNM stage, clinicopathological parameters, immunohistochemical technique, COX2 expression, and patient survival results from each study were all documented. Study quality was assessed independently by two investigators, by means of reading and evaluating according to the Newcastle-Ottawa Scale (NOS) quality assessment scale [24]. Briefly, the overall star assessed three main categories in the following: (1) subject selection: 0–4; (2) comparability of subject: 0–2; (3) clinical outcome: 0–3. NOS scores ranged from 0 to 9; and a score ≥ 7 indicates a good quality. The total number of grades was accumulated at last, with more sensitivity reflecting a better methodological quality.

2.4. Statistical Analysis. We extracted and combined the data of COX2 expression and prognostic parameters associated with oral cancer from studies and made a meta-analysis. The Version 12.0 STATA statistical software (Stata Corporation, College Station, TX, USA) was employed in this study to achieve statistical analysis. For quantitative evaluation of OS results, OR and its corresponding 95% confidence interval (95% CI) were used to estimate the influence of COX2 expression on OS of oral cancer patients. The Z test was adopted to calculate the statistical significance of pooled HR and ORs. Heterogeneity among studies was estimated.
by Cochran’s Q-statistic and I² tests [25]. A random-effect model was used when Q-test exhibits a $P < 0.05$ or $I^2$ test shows > 50%; otherwise, the fixed-effect model was used. We also make use of subgroup analyses to explore sources of heterogeneity. For the purpose of evaluating the influence of single studies on the overall estimate, a sensitivity analysis was performed. Funnel plots and Egger’s linear regression test were applied to explore the potential publication bias [26].

### 3. Result

#### 3.1. Characteristics of Included Studies.

Initially, the highly sensitive search strategy identified 264 articles. After a rough review of the titles and abstracts of all the articles, we further excluded 136 articles; The original search yielded a total of 264 papers related to the searched keywords. Through the step of screening the title and key words, 139 of these articles were excluded. Full-text from 125 articles was reviewed and an additional 111 trials were excluded, leaving 14 studies for further review. Of these, 2 were abandoned because of not supplying enough information (Figure 1). Another 2 studies were also excluded due to lack of data integrity (Figure 1). Eventually, 12 clinical cohort studies with a total of 979 oral cancer patients met our inclusion criteria for quantitative data analysis [8, 11, 18, 19, 21–23, 27–31]. There were 5 independent analyses focused on the prognosis of oral cancer, some of which were divided into two groups, including COX2-positive group ($n = 157$) and COX2-negative group ($n = 254$). Additionally, there existed 7 articles focused on protein expression of COX2, with a total of 419 oral cancer patients. As shown in Figure 2, the publication years of the eligible studies ranged from 2001 to 2013. Overall, 9 studies were conducted among Asians and the other 3 among Caucasians. Meanwhile, Envision, streptavidin-biotin-peroxidase complex (SABC), activity-based costing (ABC), streptavidin-peroxidase (SP), and Power Vision∼(TM)-9000 (PV-9000) methods were utilized in the current meta-analysis. NOS scores of all included studies were $\geq 6$. We summarized the
baseline characteristics and methodological quality in Tables 1 and 2.

3.2. Quantitative Data Synthesis. There were altogether 12 studies included focusing on the relationship between the expression of COX2 and the prognosis of oral cancer. The present meta-analysis indicated that the expression of COX2 protein in cancer tissues was significantly higher than those in normal and benign tissues (cancer tissues versus normal tissues: OR = 92.86, 95% CI = 53.61–160.84, \( P < 0.001 \); cancer tissues versus benign tissues: OR = 11.58, 95% CI = 6.68–20.08, \( P < 0.001 \), resp.). Considering the OS rate, our findings showed that COX2-positive group had a poor OS rate of oral cancer patients as compared to the COX2-negative group (HR = 2.23, 95% CI = 1.42–3.05, \( P < 0.001 \)) (Figure 3).

Subgroup analysis based on sample size and detection method revealed that the expression of COX2 in the cancer tissues was correlated with the prognosis of oral cancer patients compared to those in the normal tissues and benign tissues in all these subgroups (all \( P < 0.05 \)) (Figure 4).
Furthermore, subgroup analyses by sample size and detection method also indicated that elevated expression of COX2 protein was strongly linked to shorter OS of oral cancer patients in all these subgroups (all P < 0.05).

A sensitivity analysis indicated that the overall pooled ORs and HRs could not be affected by single study (Figure 5). There was evidence for asymmetry in the funnel plots in the comparison of cancer tissues with normal and benign tissues; Egger’s test showed a remarkable evidence of publication bias (all P < 0.05). However, with respect to the OS of oral cancer patients, there was no strong evidence in the funnel plots, and Egger’s test also failed to present any evidence of publication bias (t = 0.78, P = 0.490) (Figure 6).

4. Discussion

The purpose of this meta-analysis was to investigate the association between the expression of COX2 protein and the clinical outcome in patients with oral cancer. Our results showed that there were significant correlations between COX2 protein expression and the recurrence-free or OS rate of oral cancer, suggesting that COX2 protein expression may have a prognostic significance in oral cancer. It is widely recognized that the use of nonsteroid anti-inflammatory drugs (NSAIDs) is closely correlated with a reduced risk of cancer [32]. Exactly, COX2 is the best known target of NSAIDs, which is considered as a critical rate-limiting enzyme in the arachidonic acid metabolism that is implicated in the biosynthesis of prostaglandins [33]. Moreover, prostaglandins have been documented to have a key role in creating a proangiogenic microenvironment in human tumors [34]. In addition, COX2 has been widely known as one of the crucial prognostic factors in carcinomas of the various organs [35, 36]. However, the importance of COX2 overexpression in oral cancer has not been fully described yet. As a matter of fact, the expression of COX2 protein was supported to be low or nondetectable in most human healthy tissues, whereas it can be highly stimulated in response to cell activation by proinflammatory cytokines, growth factors, hormones, or tumor promoters [18]. Most importantly, through different mediators, the alteration in COX2 expression may promote angiogenesis, increase cancer invasiveness and metastasis, regulate cell proliferation, and inhibit apoptosis and immune surveillance [37]. To be specific, the upregulation of COX2, at both mRNA and protein levels, may result in the enhanced synthesis of prostaglandins, increasing proliferative activity of neoplastic cells, and further accelerating angiogenesis and inhibiting immune surveillance; additionally, immunohistochemical overexpression of COX2 may thereby inhibit apoptosis and strength invasiveness [27]. In this regard, high expression levels of COX2-derived prostaglandin can be identified to be active in highly vascularized tumors, and in turn selective suppression of COX2 could lead to a decreased tumor growth because of the transformation in the neovascularure [23]. Therefore, we can postulate that the elevated expression of COX2 may have an important role in predicting the clinical outcome in oral cancer, and these many essential processes in carcinogenesis make COX2 an attractive therapeutic target. In consistence with our results, Cha et al. detected the expression of COX2 via immunohistochemistry analyses of 103 OSCC samples indicating that the upregulated COX2
expression in oral cell lines may be a possible prognostic parameter for reduced overall survival [19]. Similarly, Sakurai et al. also found that the expression of COX2 was related to lymph node metastasis and cell proliferative activity, as well as overall 5-year survival rate in oral carcinoma, and thereby this enzyme may be valuable in diagnostic and prognostic indices in oral carcinoma [11].

Meanwhile, there did exist some limitations in the current meta-analysis. Firstly, due to a myriad of necessary information which cannot be successfully obtained, we did not...
Take into account unpublished articles and abstract entirely. In this regard, our results did not implicate all the data from all trials to evaluate the impact of COX2 expression on the prognostic influence of oral cancer patients. Nevertheless, our meta-analysis managed to overcome limits of size or scope in individual studies to acquire more reliable and general information from each study. Secondly, the results of meta-analysis might slightly lack reliability to some extent since it is a retrospective study, which may induce potential publication bias. Particularly we picked up those eligible English studies only because of excluding parts of qualified studies based on language criteria. A third potential limitation is that our meta-analysis may still be underpowered to acquire original data from the included studies. Despite the above limitations, this is the first example of meta-analysis on the association of COX2 expression with the development of oral cancer. With the application of a statistical approach to combine the results from multiple studies in our meta-analysis and to achieve strong objectivity, all the research methods were carried out on strict inclusion and exclusion criteria. In addition, inconsistency of results was rigorously quantified and analyzed in our meta-analysis, which will finally contribute to a more reliable conclusion.

In conclusion, our results provide empirical evidence that COX2 protein expression may be negatively correlated with a worse prognosis in patients with oral cancer. Thus, expression of COX2 protein may be regarded as a prognostic factor for oral cancer patients relying on the present obtained data. However, larger clinical studies should be performed to explore the precise prognostic significance of COX2, and the determination of its nuclear and subcellular location should also be seriously considered in particular.

**Conflict of Interests**
The authors have declared that no competing interests exist.

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Cancer tissue versus normal tissue
(Egger's test: $t = 5.62$, $P = 0.001$)

Cancer tissue versus benign tissue
(Egger's test: $t = 5.48$, $P = 0.002$)

Overall survival
(Negative versus positive)
(Egger's test: $t = 0.78$, $P = 0.490$)

Figure 6: Funnel plot of publication biases on the relationships of abnormal COX2 protein expression with clinicopathological characteristics and prognosis of patients with oral cancer.

References

[1] P. Brocklehurst, O. Kujan, L. A. O'Malley, G. Ogden, S. Shepherd, and A. M. Glenny, "Screening programmes for the early detection and prevention of oral cancer," Cochrane Database of Systematic Reviews, vol. 11, Article ID CD004150, 2013.

[2] S. Warnakulasuriya, "Global epidemiology of oral and oropharyngeal cancer," Oral Oncology, vol. 45, no. 4-5, pp. 309–316, 2009.

[3] A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman, “Global cancer statistics,” CA: Cancer Journal for Clinicians, vol. 61, no. 2, pp. 69–90, 2011.

[4] R. Lambert, C. Sauvaget, M. de Camargo Cancela, and R. Sankaranarayanan, “Epidemiology of cancer from the oral cavity and oropharynx,” European Journal of Gastroenterology and Hepatology, vol. 23, no. 8, pp. 633–641, 2011.

[5] Y. H. Chu, S. L. Tseng, C. W. Lin, M. H. Chien, M. K. Chen, and S. F. Yang, "Impacts of microRNA gene polymorphisms on the susceptibility of environmental factors leading to carcinogenesis in oral cancer" PLoS ONE, vol. 7, no. 6, Article ID e39777, 2012.

[6] T. T. Yen, W. D. Lin, C. P. Wang, C. C. Wang, and S. A. Liu, "The association of smoking, alcoholic consumption, betel quid chewing and oral cavity cancer: a cohort study," European Archives of Oto-Rhino-Laryngology, vol. 265, no. 11, pp. 1403–1407, 2008.

[7] S. Petti, "Lifestyle risk factors for oral cancer," Oral Oncology, vol. 45, no. 4-5, pp. 340–350, 2009.

[8] T. J. Li and J. Cui, "COX-2, MMP-7 expression in oral lichen planus and oral squamous cell carcinoma," Asian Pacific Journal of Tropical Medicine, vol. 6, no. 8, pp. 640–643, 2013.

[9] A. Greenhough, H. J. M. Smartt, A. E. Moore et al., “The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment,” Carcinogenesis, vol. 30, no. 3, pp. 377–386, 2009.

[10] C. Carli, C. N. Metz, Y. Al-Abed, P. H. Naccache, and A. Akoum, "Up-regulation of cyclooxygenase-2 expression and prostaglandin E2 production in human endometriotic cells by macrophage migration inhibitory factor: involvement of novel kinase signaling pathways," Endocrinology, vol. 150, no. 7, pp. 3128–3137, 2009.

[11] K. Sakurai, M. Urade, K. Noguchi et al., "Prognostic significance of cyclooxygenase-2 and DNA topoisomerase IIa expression in oral carcinoma," Head and Neck, vol. 29, no. 11, pp. 1002–1009, 2007.
[12] D. Wang and R. N. Dubois, “The role of COX-2 in intestinal inflammation and colorectal cancer,” Oncogene, vol. 29, no. 6, pp. 781–788, 2010.

[13] E. Looby, M. M. M. Abdel-Latif, V. Athié-Morales, S. Duggan, A. Long, and D. Kelleher, “Deoxycholate induces COX-2 expression via Erk1/2-, p38-MAPK and AP-1-dependent mechanisms in esophageal cancer cells,” BMC Cancer, vol. 9, article 190, 2009.

[14] R. E. Harris, “Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung,” Inflammopharmacology, vol. 17, no. 2, pp. 55–67, 2009.

[15] W. Bartchewsky Jr., M. R. Martini, M. Masiero et al., “Effect of Helicobacter pylori infection on IL-8, IL-1β and COX-2 expression in patients with chronic gastritis and gastric cancer,” Scandinavian Journal of Gastroenterology, vol. 44, no. 2, pp. 153–161, 2009.

[16] X. Wang, J. K. L. Colby, R. C. Rengel, S. M. Fischer, S. K. Clinton, and R. D. Klein, “Overexpression of cyclooxygenase-2 (COX-2) in the mouse urinary bladder induces the expression of immune- and cell proliferation-related genes,” Molecular Carcinogenesis, vol. 48, no. 1, pp. 1–13, 2009.

[17] J. Y. Baek, W. Hur, J. S. Wang, S. H. Bae, and S. K. Yoon, “Selective COX-2 inhibitor, NS-398, suppresses cellular proliferation in human hepatocellular carcinoma cell lines via cell cycle arrest,” World Journal of Gastroenterology, vol. 13, no. 8, pp. 1175–1181, 2007.

[18] T. Atula, J. Hedström, A. Ristimäki et al., “Cyclooxygenase-2 expression in squamous cell carcinoma of the oral cavity and pharynx: association to p53 and clinical outcome,” Oncology Reports, vol. 16, no. 3, pp. 485–490, 2006.

[19] J. D. Cha, S. Li, and I. H. Cha, “Association between expression of embryonic lethal abnormal vision-like protein HuR and cyclooxygenase-2 in oral squamous cell carcinoma,” Head and Neck, vol. 33, no. 5, pp. 627–637, 2011.

[20] M. Pandey, O. Prakash, W. S. Santhi, C. S. Soumithran, and R. M. Pillai, “Overexpression of COX-2 gene in oral cancer is independent of stage of disease and degree of differentiation,” International Journal of Oral and Maxillofacial Surgery, vol. 37, no. 4, pp. 379–383, 2008.

[21] X. P. Cao, S. T. Zhang, H. Zhou, H. Y. Wu, X. J. Liu, and Y. Y. Zhang, “Relationship between the expression of cyclooxygenase-2 and microvessel density in oral squamous cell carcinoma,” West China Journal of Stomatology, vol. 23, pp. 431–433, 2005.

[22] J. Sudbo, A. Ristimäki, J. E. Sondresen et al., “Cyclooxygenase-2 (COX-2) expression in high-risk premalignant oral lesions,” Oral Oncology, vol. 39, no. 5, pp. 497–505, 2003.

[23] M. C. Haffner, J. Laimer, A. Chaux et al., “High expression of prostate-specific membrane antigen in the tumor-associated neo-vasculature is associated with worse prognosis in squamous cell carcinoma of the oral cavity,” Modern Pathology, vol. 25, no. 8, pp. 1079–1085, 2012.

[24] A. Stang, “Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses,” European Journal of Epidemiology, vol. 25, no. 9, pp. 603–605, 2010.

[25] E. Zintzaras and J. P. A. Ioannidis, “HEGESMA: genome search meta-analysis and heterogeneity testing,” Bioinformatics, vol. 21, no. 18, pp. 3672–3673, 2005.

[26] J. L. Peters, A. J. Sutton, D. R. Jones, K. R. Abrams, and L. Rushton, “Comparison of two methods to detect publication bias in meta-analysis,” The Journal of the American Medical Association, vol. 295, no. 6, pp. 676–680, 2006.

[27] S. Itoh, K. Matsui, I. Furuta, and Y. Takano, “Immunohistochemical study on overexpression of cyclooxygenase-2 in squamous cell carcinoma of the oral cavity: its importance as a prognostic predictor,” Oral Oncology, vol. 39, no. 8, pp. 829–835, 2003.

[28] E. Segawa, K. Sakurai, H. Kishimoto et al., “Expression of cyclooxygenase-2 and DNA topoisomerase IIα in precancerous and cancerous lesions of the oral mucosa,” Oral Oncology, vol. 44, no. 7, pp. 664–671, 2008.

[29] M. Sawhney, N. Rohatgi, J. Kaur et al., “Expression of NF-kB parallels COX-2 expression in oral precancer and cancer: association with smokeless tobacco,” International Journal of Cancer, vol. 120, no. 12, pp. 2545–2556, 2007.

[30] D. W. Tang, S. C. Lin, K. W. Chang, C. W. Chi, C. S. Chang, and T. Y. Liu, “Elevated expression of cyclooxygenase (COX-2) in oral squamous cell carcinoma—evidence for COX-2 induction by areca quid ingredients in oral keratinocytes,” Journal of Oral Pathology and Medicine, vol. 32, no. 9, pp. 522–529, 2003.

[31] K. Sakurai, M. Urade, K. Noguchi et al., “Increased expression of cyclooxygenase-2 in human salivary gland tumors,” Pathology International, vol. 51, no. 10, pp. 762–769, 2001.

[32] C. Cuzick, F. Otto, J. A. Baron et al., “Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement,” The Lancet Oncology, vol. 10, no. 5, pp. 501–507, 2009.

[33] S. H. Choi, S. Aid, and F. Bosetti, “The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research,” Trends in Pharmacological Sciences, vol. 30, no. 4, pp. 174–181, 2009.

[34] H. Katoh, K. Hosono, Y. Ito et al., “COX-2 and prostaglandin EP3/EP4 signaling regulate the tumor stromal proangiogenic microenvironment via CXCL12-CXCR4 chemokine systems,” The American Journal of Pathology, vol. 176, no. 3, pp. 1469–1483, 2010.

[35] S. Meyer, T. Vogt, M. Landthaler et al., “Cyclooxygenase 2 (COX2) and peroxisome proliferator-activated receptor γ (PPARG) are stage-dependent prognostic markers of malignant melanoma,” PPAR Research, vol. 2010, Article ID 848645, 11 pages, 2010.

[36] J. Mrena, J. Wiksten, A. Kokkola, S. Nordling, A. Ristimäki, and C. Haglund, “COX-2 is associated with proliferation and apoptosis markers and serves as an independent prognostic factor in gastric cancer,” Tumor Biology, vol. 31, no. 1, pp. 1–7, 2010.

[37] M. Şahin, E. Şahin, and S. Gümüşlü, “Cyclooxygenase-2 in cancer and angiogenesis,” Angiology, vol. 60, no. 2, pp. 242–253, 2009.