Original Article

The Expression of Cyclooxygenase-2 in Carcinoma of Uterine Cervix

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Abstract

Background: Cancer of the cervix is the second leading cause of cancer deaths in women worldwide and remains a leading cause of mortality among women of reproductive age in developing countries. In India, 27% deaths is attributed to cervical cancer among females between 15 and 44 years of age. Studying the expression of COX-2 in cancer tissues and its role in the growth of malignant tumours is important because NSAIDs might help to prevent cancer. Furthermore, selective COX-2 inhibitors are available that block the effects of COX-2 expression but spare the expression of COX-1. **Aim and Objectives:** The aim of our study is to classify carcinoma of uterine cervix using WHO criteria and to determine the differential expression pattern of cyclooxygenase-2 (COX-2) in carcinoma cervix and to compare this expression with clinicopathological parameters. **Materials and Methods:** A total of hundred (100) cases of cervical carcinoma were included in the study material submitted as cervical biopsies or hysterectomy specimens in the Department of Pathology, The tissue block was sectioned at 4-5 µm and the sections were stained for Haematoxylin and Eosin stains (H and E). The tumours were classified and graded using the WHO criteria. Immunohistochemistry was performed on the representative sections with COX-2 antibodies using standard protocols. Cases of colon cancer were taken as positive control and negative control were obtained by omitting the primary antibody in the staining protocol. Positive cases showed cytoplasmic positivity. The raw data was converted to immunohistochemical score (IHC Score) by multiplying the quantity and staining intensity scores. The scores theoretically ranged from 0-12. Score of 0-3 was considered Negative, 4-8- Moderate and 9-12 as Strong. Using the Chi-square test the distribution of COX-2 positive cases was analysed according to clinicopathological features. *P*-value < 0.05 was regarded as statistically significant. **Results:** In our study there was a significant correlation observed between expression of COX-2 and inflammation. No significant correlation was found between other parameters. **Conclusion:** The data suggests that COX-2 induction may play a role in high cervical inflammation and carcinogenesis. The patients with a high COX-2 expression could possibly be benefitted with more individualized treatments such as COX-2 inhibitors

Keywords: *Biopsy, carcinoma cervix, cyclooxygenase, inflammation*

Introduction

Cancer of the cervix is the second leading cause of cancer deaths in women worldwide and remains a leading cause of mortality among women of reproductive age in developing countries.[1] An estimated 530,000 new cases with 270,000 deaths occurred due to cervical cancer worldwide according to one recent analysis. Eighty-five percent of deaths due to cervical cancer occur in developing countries.

In India, 27% deaths are attributed to cervical cancer among females between 15 and 44 years of age. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from disease. India has a population of 432.2 million women aged 15 years and older who are at risk of developing cancer. It is second-most common cancer in women aged 15–44 years. India also has the highest age standardized incidence of cervical cancer in South Asia at 22, compared to 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran.[2]

Two prophylactic human papillomavirus (HPV) vaccines have been developed. Both the vaccines are based on recombinant expression and self-assembly of the major capsid protein, L1, virus like particles. Gardasil protects against HPV type 6, 11, 16, and 18 (quadrivalent) and other Cervarix protects against type 16 and 18 (bivalent). The goal of prophylactic vaccines is to reduce the incidence of HPV-related genital disease and precancerous lesions.[3]

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Most cervical cancers arise at the squamocoloumnar junction where continuous metaplastic changes take place. Maximum metaplastic activity occurs during active sexual life. The incidence rate rises in 30–34 years of age group and peaks at 55–65 years. The major risk factors for carcinoma cervix include viral infections (HPV, human immunodeficiency virus, herpes simplex virus), early onset of sexual activity, multiple sexual partners, or engaging in sexual activity with promiscuous men and history of sexually transmitted infections.[4]

The role of cyclooxygenase-2 (COX-2) in carcinogenesis and tumor progression has been a subject of a lot of research. COX enzyme exists in two main isoenzyme forms. COX-1 is expressed in most of the tissues and catalyzes the synthesis of prostaglandins from arachidonic acid, which are required for normal, physiologic functions, for example, gastrointestinal cytoprotection and platelet activity. It is also expressed in endothelial cells and renal microvasculature. COX-2 is not detectable in most normal tissues and basal conditions. It is induced by cytokines (inflammatory response), growth factors, and tumor promoters.[5,6]

COX-2 is overexpressed in many cell types such as macrophages, epithelial, endothelial cells, fibroblast, and thus contributes to increased prostaglandins synthesis in inflamed and neoplastic tissues.[7,8] COX-2 overexpression was observed in early carcinogenesis in colon cancer and carcinogenesis suppression was observed in mice disable of COX-2 gene. COX-2 overexpression has been noticed in different types of cancer including pancreatic, lung, breast, colorectal, esophageal, gastric, bladder, ovary, endometrial, and cervix cancer.[9]

Studying the expression of COX-2 in cancer tissues and its role in the growth of malignant tumors is important because nonsteroidal anti-inflammatory drugs might help to prevent cancer. Furthermore, selective COX-2 inhibitors are available that block the effects of COX-2 expression but spare the expression of COX-1.[5]

The aim of our study is to classify carcinoma of uterine cervix using the World Health Organization (WHO) criteria and to determine the differential expression pattern of COX-2 in carcinoma cervix and to compare this expression with clinicopathological parameters.

Material and Methods

A total of 100 cases of cervical carcinoma were included in the study material submitted as cervical biopsies or hysterectomy specimens in the Department of Pathology, Pt. B. D. Sharma, University of Health Sciences, Rohtak. Following standard protocols the tissue was fixed in buffered formalin (pH = 7.0), and embedded in paraffin. The tissue block was sectioned at 4–5 μm and the sections were stained for hematoxylin and eosin stains (H and E).[10] The tumors were classified and graded using the WHO criteria.[11] Histochemical stains such as periodic acid-Schiff, mucicarmine, and alcian blue were used wherever required. Immunohistochemistry was performed on the representative sections with COX-2 antibodies using standard protocols. Cases of colon cancer were taken as positive control and negative control were obtained by omitting the primary antibody in the staining protocol.

Interpretation

Positive cases showed cytoplasmic positivity.[12] The immunoreactive cells (quantity score) were estimated as: Score 0-staining observed in 0%–5% cells. Score 1-staining observed in 6%–25% cells. Score 2-staining observed in 26%–50% cells. Score 3-staining observed in 51%–75% cells. Score 4-staining observed in 76%–100% cells. Staining intensity was read on a scale of 0–3:0-Negative, 1-Weak, 2-Moderate, and 3-Strong. With multifocal immunoreactivity and significant difference in staining intensities between foci, the average of least intense and most intense staining was recorded. The raw data were converted to immunohistochemical score (IHC score) by multiplying the quantity and staining intensity scores. The scores theoretically ranged from 0 to 12.

- IHC score Immunoreactivity
- 0–3 Negative
- 4–8 Moderate
- 9–12 Strong

Using the Chi–square test, the distribution of COX-2-positive cases was analyzed according to clinicopathological features. $P < 0.05$ was regarded as statistically significant.

Results

A total of 100 cases of cervical cancer were included in our study of which 34 were hysterectomy specimens. Of total cases, (53%) in the age group of 40–60 years were postmenopausal. It was observed that maximum number of cases (79%) were of squamous cell carcinoma, followed by 13% cases of adenocarcinoma, (3%) cases were of cervical intraepithelial neoplasm (CIN) and adenosquamous carcinoma each and (2%) cases were the other histological variants such as large cell neuroendocrine carcinoma and clear cell carcinoma [Table 1]. In our study, maximum cases (61%) showed moderate immunoreactivity, followed by 34% which were negative and only 5% showed strong expression [Table 2].

The expression of COX-2 was studied in all histological subtypes separately. Seventy-nine cases belonged to squamous cell carcinoma in which 63.3% of cases showed moderate expression of COX-2, 32.91% cases were negative and 3.8% showed strong expression. Of 13 cases of adenocarcinoma, 53.8% showed moderate expression. No significant correlation was seen in COX-2 expression and histological subtypes ($P = 0.091$) [Table 3 and Figure 1]. In 79 cases of squamous cell carcinoma, the expression of COX-2 was studied in relation to histological grades of

differentiation. Sixty-three (63.3%) cases showed moderate expression of C0X-2. Of 79 cases, (62.5%) cases of well differentiated squamous cell carcinoma (WDSCC), 69.5% cases of moderately differentiated squamous cell carcinoma (MDSCC), and 33.3% cases of poorly differentiated squamous cell carcinoma (PDSCC) showed moderate expression. However, no significant correlation was seen in COX-2 and grades of differentiation ($P = 0.059$).

In our study, 52 (52%) cases showed the presence of inflammation of which 71.1% showed moderate COX-2 expression. Forty-eight (48%) cases did not show any evidence of inflammation and in these cases, 50% showed moderate expression of C0X-2. The 5% of cases showing strong expression of COX-2, all had significant inflammation. Therefore, a significant association was seen between expression of COX-2 and presence of inflammation ($P = 0.001$) [Table 4].

Table 1: Distribution of cases of carcinoma cervix according to who classification

WHO classification	Number of cases (out of 100) (%)
Squamous cell carcinoma, *n*=79, *n* (%)	79 (79)
WDSCC	8 (10.1)
MDSCC	59 (74.7)
PDSCC	12 (15.2)
Adenocarcinoma	13 (13)
Adenosquamous carcinoma	3 (3)
CIN	3 (3)
Others (large cell neuroendocrine and clear cell carcinoma)	2 (2)

MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma, WDSCC: Well differentiated squamous cell carcinoma, CIN: Cervical intraepithelial neoplasm

Table 2: Distribution of cases according to immunoreactivity

Immunohistochemical score	Immunoreactivity	Number of cases (*n*=100), *n* (%)
0-3	Negative	34 (34)
4-8	Moderate	61 (61)
9-12	Strong	5 (5)
Total		100

Various clinicopathological parameters such as age, menstrual status, inflammation, and lymph node involvement were compared in 79 cases of squamous cell carcinoma out of total 100 cases. The mean age of COX-2-positive cases was (52.81 ± 13.77) years. A significant correlation was seen between COX-2 expression and inflammation ($P = 0.002$). There was no significant correlation between COX-2 expression and age ($P = 0.731$), menstrual status ($P = 0.937$), and lymph node involvement ($P = 0.073$) [Table 5].

Similarly, clinicopathological parameters were studied in 13 cases of adenocarcinoma. The median age of positive cases was (51.88 ± 9.48) years. No significant correlation was obtained between expression of COX-2 and age ($P = 0.915$), menstrual status ($P = 0.725$), inflammation ($P = 0.429$), and lymph node involvement ($P = 0.188$) [Table 6].

Discussion

Cancer of cervix is the second leading cause of cancer deaths in women worldwide and remains a leading cause of mortality among women or reproductive age group in developing countries. Cervical carcinoma arises in women infected with HPV[13,14] and progress through a multistage process of carcinogenesis. Because premalignant phase of cervical carcinogenesis may last for 5–10 years, it is ideally suited for chemopreventive therapy.

A large body of evidence suggests that COX-2 is important in carcinogenesis.[15] In addition to the genetic evidence implicating COX-2 carcinogenesis, there are supporting pharmacological data. Selective COX-2 inhibitors suppressed the formation of variety of tumors in experimental animals.[16]

In the present study, female patients of all ages were included ranging from 25 to 86 years. Majority of cases (53%) belonged to 40–60 years of age. The median age of patients was 55 years. The mean age of patients with squamous cell carcinoma was 52.81 ± 13.77 years and that of adenocarcinoma was 51.88 ± 9.48 years. Likewise, Kim *et al.*[17] in 2004, evaluated 105 patients belonging to age range of 25–75 years. The median age for squamous cell carcinoma was 54.0 years and for adenocarcinoma was 58.0 years. Khunamornpong *et al.* also reported similar results in their study.[18]

Table 3: Correlation of cyclooxygenase-2 expression according to histological types

WHO classification	Negative	Moderate	Strong	*P*
SCC (*n*=79) (100%)	26 (32.9)	50 (63.3)	3 (3.8)	0.091
Adenocarcinoma (*n*=13) (100%)	5 (38.5)	7 (53.8)	1 (7.7)	
Adenosquamous (*n*=3)	-	2	1	
CIN (*n*=3)	3	-	-	
Others (*n*=2)	-	2	-	
Total (*n*=100)	34	61	5	

SCC: Squamous cell carcinoma, CIN: Cervical intraepithelial neoplasm

Table 4: Correlation of cyclooxygenase-2 expression with inflammation

Inflammation	Negative, *n* (%)	Moderate, *n* (%)	Strong, *n* (%)	*P*
Present (*n*=52) (100%)	10 (19.2)	37 (71.1)	5 (9.6)	0.001
Absent (*n*=48) (100%)	24 (50.0)	24 (50.0)	0 (0)	
Total (*n*=100)	34	61	5	

Table 5: Expression of cyclooxygenase-2 in squamous cell carcinoma with various clinicopathological parameters

Variables	Expression of COX-2 in SSC		*P*
	Negative	Positive	
Age (mean±SD)	51.69±13.01	52.81±13.77	0.731
Menstrual status			
Yes	13	26	0.937
No	13	27	
Inflammation			
Yes	7	34	0.002
No	19	19	
Lymph node involvement			
Yes	2	13	0.073
No	24	40	

SD: Standard deviation, COX-2: Cyclooxygenase-2, SCC: Squamous cell carcinoma

Table 6: Expression of cyclooxygenase-2 in adenocarcinoma with various clinicopathological parameters

Variables	Expression of COX-2 in adenocarcinoma		*P*
	Negative	Positive	
Age (mean±SD)	51.20±13.03	51.88±9.48	0.915
Menstrual status			
Yes	3	4	0.725
No	2	4	
Inflammation			
Yes	2	5	0.429
No	3	3	
Lymph node involvement			
Yes	1	0	0.188
No	4	8	

SD: Standard deviation, COX-2: Cyclooxygenase-2

A total of 100 cases were studied in which 79% of cases were of squamous cell carcinoma, followed by 13% cases of adenocarcinoma, 3% cases of adenosquamous, 3% cases of CIN, and 2% included cases of large cell neuroendocrine and clear cell carcinoma. Various histological subtypes diagnosed in the other studies,[19] Gaffney *et al.*,[20] and Kim *et al.*[17] were in concordance with our study. Ferrandina *et al.*[21] studied 99 cases of cervical cancer of which 82% cases were of squamous cell carcinoma, 12% cases were of adenocarcinoma, and 6% cases were adenosquamous cell carcinoma. However, Chen *et al.*[22] studied 53 cases of cervical cancer, in which 66% were squamous cell carcinoma, 32% were adenocarcinoma, and 2% were adenosquamous carcinoma. The variation in histological subtypes can be attributed to small number of cases studied or to the difference in environmental factors in the particular geographical area.

In our study, no significant correlation was observed between COX-2 expression and histological subtypes of cervical carcinoma. It was in concordance with study by Kim *et al.*[17] in which sample size (n = 105) was equivalent to that of our study. However, our study was in disconcordance with that of Ferrandina *et al.*[23] (n = 84), in which COX-2 expression was higher in adenocarcinoma than squamous cell carcinoma. Similarly, Chen *et al.*[22] (n = 22) found overexpression of COX-2 in both squamous cell carcinoma and adenocarcinoma but squamous cell carcinoma showed infrequent and low expression as compared to adenocarcinoma.

Cases of squamous cell carcinoma (n = 79) included in our study were divided into three histological grades of differentiation by applying WHO histological criteria.[11] Nearly seventy-five percent cases (74.7%) were MDSCC, 15.2% were PDSCC and 10.1% were WDSCC.

Seventy-nine (n = 79) cases of squamous cell carcinoma were classified as per histological grades of differentiation and expression of COX-2 was evaluated. The study was in concordance,[19] Ferrandina *et al.*,[23] and Khunamornpong *et al.*[18] in lacking a significant correlation of histological grade of tumor with COX-2 expression.

An association of cervicitis with high-grade cervical lesions and cervical carcinoma has been hypothesized.[24,25] The presence of intraepithelial and submucosal lymphocytes, plasma cells, and chronic inflammation was studied. In our study, 52% of cases were found to be associated with significant inflammation. Likewise, Saldivar *et al.*[26] evaluated diseased (CIN) and normal (control) biopsies from 52 patients in which 72% showed significant inflammation.

In the present study, 52% of cases showed inflammation and COX-2 positivity was high in these cases (P = 0.001). A significant correlation was seen in expression of COX-2 and cases of squamous cell carcinoma with inflammation (P = 0.002). However, in adenocarcinoma, no significant correlation could be obtained (P = 0.429). This could be attributed to a small number of adenocarcinoma cases included in the study. The results of the association of COX-2 with inflammation were in concordance with study by Saldivar *et al.*[26] They found that within control biopsy the mean COX-2 protein concentration was 3.7 times higher in inflammation positive cases than in inflammation negative cases (P = 0.05). Similarly, in abnormal biopsies the

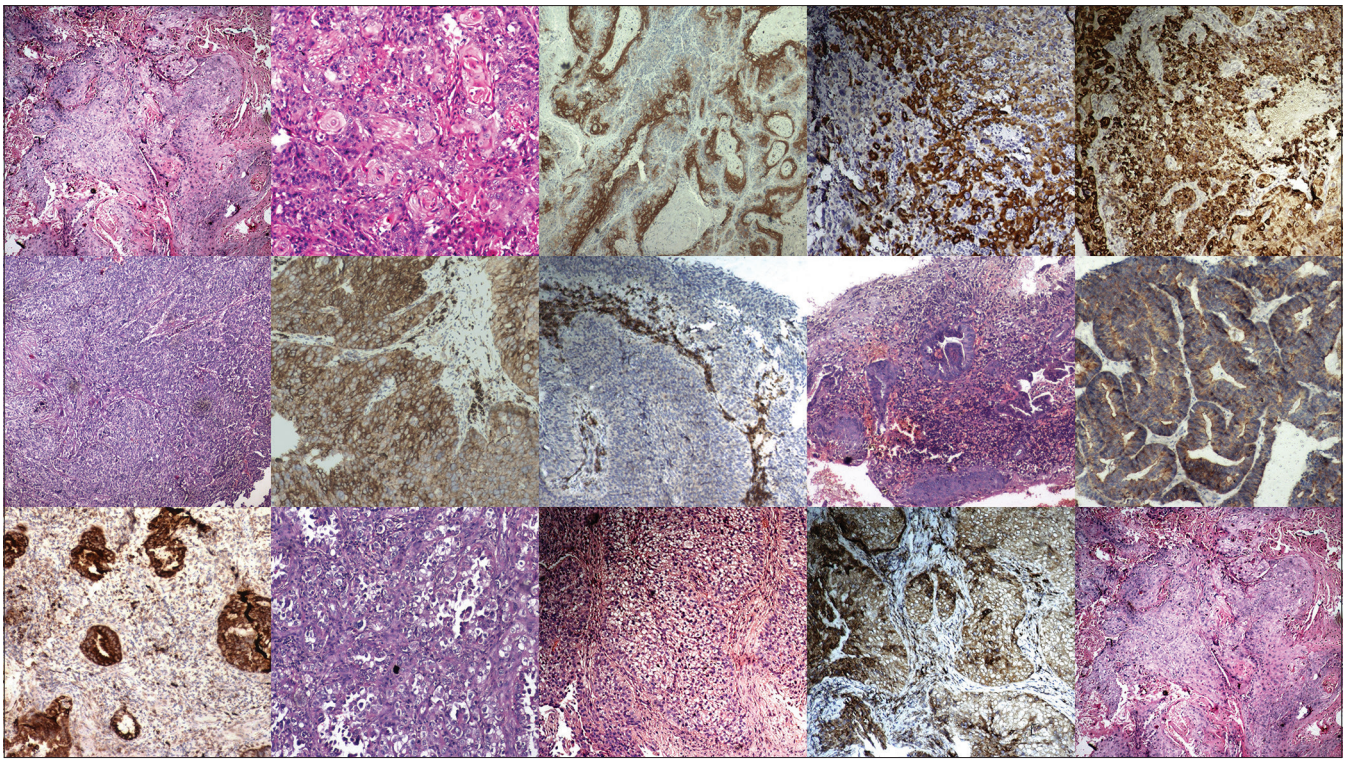

Figure 1: Row 1 (left to right): (1) Moderately differentiated squamous cell carcinoma showing keratinization and intercellular bridges (H and E, ×40). (2) Well differentiated squamous cell carcinoma showing keratinization and intercellular bridges (H and E, ×40). (3) Moderately differentiated squamous cell carcinoma (MDSCC) showing strong expression of COX-2 with strong intensity in 50%–75% cells (Immunohistochemical score 3 × 3 = 9) (IHC, ×40). (4) Moderately differentiated squamous cell carcinoma (MDSCC) showing strong expression of COX-2 with strong intensity in 50%–75% cells (Immunohistochemical score 3 × 3 = 9) (IHC, ×40). (5) Well-differentiated squamous cell carcinoma showing strong expression COX-2 staining (Immunohistochemical score 3 × 4 = 12) (IHC, ×40). Row 2 (left to right): (6) Poorly differentiated squamous cell carcinoma (PDSCC) showing marked nuclear pleomorphism (H and E, ×40). (7) Poorly differentiated carcinoma showing (PDSCC) showing moderate expression of COX-2 with moderate expression in 76%–100% cells (Immunohistochemical score 2 × 4 = 8). (8) Poorly differentiated squamous cell carcinoma (PDSCC) showing negative expression of COX-2 with no staining of tumor cells (Immunohistochemical score 0) (IHC, ×40). (9) Adenocarcinoma showing glands (H and E, ×40) and nuclear pleomorphism (H and E, ×40). (10) Adenocarcinoma showing strong expression of COX-2 with tumor cells showing strong intensity of staining in 76%–100% cells (Immunohistochemical score 3 × 4 = 12) (IHC, ×200). Row 3 (left to right): (11) Adenocarcinoma showing a negative expression of COX-2 with tumor cells showing mild intensity in 51%–75% cells (Immunohistochemical score 1 × 3 = 3) (IHC, ×200). (12) Clear cell carcinoma having clear cytoplasm and abundance of eosinophils (H and E, ×100) (13) Adenosquamous carcinoma with well-defined squamous component (H and E, ×40). (14) Adenosquamous carcinoma showing strong expression of COX-2 with strong intensity of staining in 50%–75% cells (3 × 3 = 9) (IHC, ×40). (15) Moderately differentiated carcinoma (H and E, ×40)

COX-2 expression was 11.7 times higher in inflammation positive cases as compared to inflammation negative cases ($P < 0.01$). It has been hypothesized that chronic inflammatory state in the neoplastic environment promotes tumor development through angiogenesis, tumor infiltration, and resistance to apoptosis. The mechanism by which inflammatory cells regulate angiogenesis and apoptosis is through prostaglandins signaling as a result of COX-2 induction by pro-inflammatory cytokines. In our study, there is increased COX-2 expression which is associated with increased inflammation, implicating this process in carcinogenesis.

In our study, 34 Wertheim's Hysterectomy specimens were studied for lymph node involvement. Only 16 (47.1%) cases showed tumor metastasis with no significant correlation with COX-2 expression ($P = 0.34$). The expression of COX-2 was evaluated in lymph node positive cases of squamous cell carcinoma and adenocarcinoma separately and no significant correlation was observed ($P = 0.073$) and ($P = 0.188$), respectively. Similar pattern was reported in study by Ferrandina *et al*.[23] in which no association was found between COX-2 expression an lymph node involvement. However, Khunamornpong *et al*.[18] observed that lymph node metastasis significantly correlated with COX-2 expression ($P = 0.045$) and demonstrated that COX-2 expression is associated with a greater incidence of deep stromal and parametrial invasion. The possible source of variability between our study and others could be attributed to heterogeneous patient population, a small sample size or the antibody used against COX-2 (polyclonal or monoclonal).

Conclusion

In our study, there was no significant correlation observed between COX-2 expression and various clinicopathological parameters such as age, menstrual status, histological type, grade, stage, or lymph node metastasis. However, our findings demonstrated a significant correlation between

inflammation and COX-2 expression in squamous cell carcinoma. The data suggest that COX-2 induction may play a role in high cervical inflammation and carcinogenesis. During chronic inflammation, the cycle between innate and adaptive immune system can be always regulated culminating in tissue damage, oxidative DNA damage, and subsequent carcinogenesis. The patients with a high COX-2 expression could possibly be benefitted with more individualized treatments such as COX-2 inhibitors. However, a larger number of cases may help to identify more readily any significant association between COX-2 expression and different parameters in this cancer and potential therapeutic role of COX-2 inhibitors in such cases.

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Conflicts of interest

There are no conflicts of interest.

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