

Review

## Impact of Cyclooxygenase-2 in Breast Cancer

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**Abstract.** Prostaglandin metabolism plays a pivotal role in inflammatory processes and has also been demonstrated to have a role in carcinogenesis, tumor differentiation and tumor growth in breast cancer. Cyclooxygenase-2 (COX-2) is the key involved enzyme, as it triggers prostaglandin synthesis. We reviewed the current literature regarding the impact of prostaglandin metabolism on breast cancer and illustrated the current evidence of the COX-2 influence on breast cancer, delineating possible future prophylactic and therapeutic strategies.

Comprising 28.9 % of all carcinomas and 17.6 % of total cancer deaths of women in Europe, breast cancer is the most significant malignancy in females (1). The molecular characterization of the malignancy is an indicator for tumor prognosis and aggressiveness and may contribute to routine clinical decision making. Additionally, identifying specific molecular patterns helps to introduce individually targeted therapies for cancer treatment (2, 3). Classical molecular prognostic parameters of breast cancer are estrogen and progesterone receptor expression and HER-2 receptor expression (2, 3). Furthermore, increased levels of urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1) correlate with a poor outcome in breast cancer (4). Recent studies have defined new biomarkers correlated to a poor prognosis: prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and associated proteins in the cyclooxygenase (COX)-system (5-15). As a result, the activity of the COX system in breast

cancer is under intense evaluation. In human breast cancer, the concept of inflammation as a critical component of tumor progression has been thoroughly investigated regarding the molecular processes. It is now becoming clear that the tumor microenvironment, which is characterized by inflammatory cells, participates in the neoplastic process by fostering proliferation, survival and migration of tumor cells conducted by receptors for invasion, migration and metastasis (16). COX-2 plays a crucial role as a prognostic factor for malignancy (17) and has been associated with carcinogenesis, particularly neoangiogenesis and tumor progression (5, 9, 11-12, 14-15).

### Physiological Functions and Metabolism of COX

Prostaglandins are synthesised from free arachidonic acid by two isoenzymes: cyclooxygenase (COX) 1 and 2. COX-1 and -2 trigger the catabolism of arachidonic acid to prostaglandin G<sub>2</sub> (PGG<sub>2</sub>). PGG<sub>2</sub> is converted to prostaglandin H<sub>2</sub> (PGH<sub>2</sub>) by a glutathione-dependent peroxidase. PGH<sub>2</sub> constitutes the basic metabolite for different subtypes of prostaglandins which are involved in inflammatory processes (18). These different subtypes of prostaglandins are synthesised by microsomal or cytosolic prostaglandin synthases which are specific in different cells and tissues. Prostaglandin E synthase (PGES) triggers the conversion of PGH<sub>2</sub> to PGE<sub>2</sub> (Figure 1). Prostaglandins are synthesised in a variety of different tissues and act as autocrine and paracrine factors. Different subtypes of prostaglandins are generated according to the specific subtypes of enzymes in a specific cell (19). Prostaglandins exert their function by ligand binding to specific prostaglandin receptors. These receptors are G-protein receptors; for example, signal transduction induced angiogenesis. Prostaglandins are catabolized by 15-hydroxy-prostaglandin dehydrogenase (15-PGDH). Thus, as the key enzymes of arachidonic acid metabolization, COX-1 and -2 play pivotal roles in inflammatory processes. COX-1 is expressed ubiquitously but it does not constitute a significant

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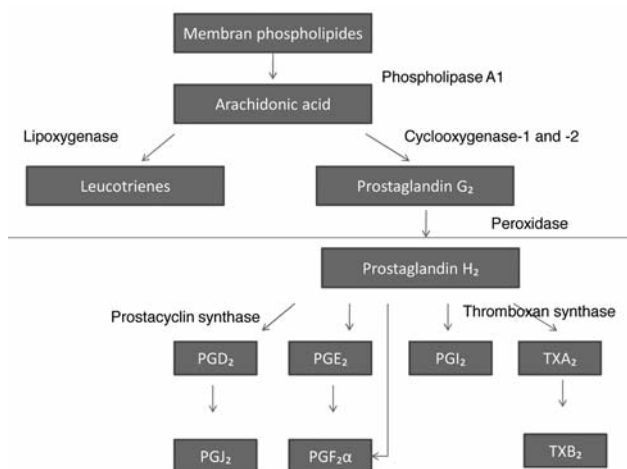


Figure 1. Prostaglandin metabolism. Abbreviations: PG=Prostaglandin; TX=Thromboxan.

factor for prognosis (20). However the pro-inflammatory enzyme COX-2 is expressed in distinct tissues and its expression is induced and regulated by growth factors, tumor promoters, cytokines, hormones and prostaglandins and is involved in inflammatory processes (17). Both cyclooxygenases are encoded by genes which are located on different chromosomes and are tightly regulated (21). *In vivo* studies using *COX-1*- and *COX-2*-knock-out mice contribute to further insight in the specific functions of both isoenzymes (22). *COX-2*-knock out mice showed *inter alia* multiple reproduction disorders, *e.g.* anovulation, disorders in fertilisation, implantation and of decidualisation due to a lack of ovarian PGE<sub>2</sub> (23). Substitution of PGE<sub>2</sub> resulted in reconstitution of ovarian function (24). These observations corroborated the hypothesis that COX-2 plays an important role in ovarian function. Furthermore the enzyme is integral to the cardiovascular system development. A total of 35% of all *COX-2*-knock-out mice died within 48 h post partum due to *ductus arteriosus apertus* (25). Non-steroidal anti-inflammatory drugs (NSAIDs) interfere with COX function specifically inhibiting either COX-1 or COX-2 isoforms of the enzyme. Celecoxib and rofecoxib are typical selective COX-2 inhibitors, while acetylsalicylic acid, ibuprofen and indomethacin are non-selective, inhibiting both isoforms.

### Evidence for COX-2 Influence in Breast Cancer

**Protein expression of COX-2 (immunohistochemistry, IHC).** COX-2 protein expression has been demonstrated in a variety of epithelial cancer types, *e.g.* breast (26), ovarian (27), colon (6, 7), gastric (28), oesophageal (10), prostate (11), hepatic and pancreatic cancer, and adenocarcinoma of

the lung (12). In current literature, IHC measurement of COX-2 expression is positive at an average rate of 50% of all breast carcinomas. *In vitro* studies have shown no COX-2 expression in non-invasive oestrogen-receptor (ER) positive MCF-7 breast cell lines and moderate expression in invasive MDA-MB-231 breast cells. Other studies have analyzed ER-negative MDA-MB-435 and MDA-MB-468 cells. The level of COX-2 expression has been found to have a significant correlation with tumour invasiveness (26, 29-31). In breast cancer, data for COX-2 protein expression are inconsistent. Both invasive ductal and lobular breast carcinomas express COX-2, however the proportion of COX-2-positive carcinoma differs significantly in the various publications (range between 4.5 and 85%) (Table I) (32). These differences are partly attributed to different scoring systems and cut-offs (32) and, furthermore, to the fact that IHC does not deliver quantitative results. Western blot analysis and real-time PCR are alternative techniques which provide quantitative protein expression analysis; however, to date only few analyses of COX-2 expression have been based on these techniques (31, 33-34). In our recent published studies we based the measurement of COX-2 protein expression on western blot analysis and found a two-fold higher COX-2 expression in non-invasive MCF-7 breast cancer cells in comparison to benign MCF-10F breast cells (35) and a more than 4-fold higher COX-2 protein levels ( $p < 0.01$ ) in the malignant tissue as compared to the normal tissue samples.

**mRNA expression of COX-2.** Data for *COX-2* mRNA expression in breast cancer are also inconsistent and range from 50 to 100% (Table II) (32). We conducted comparative studies of COX-2 protein expression and *COX-2* mRNA expression in invasive breast cancer cell lines (35) and breast cancer tissue (36) by western blot analysis and real-time PCR. Results in the cell line study were divergent. We found significantly lower *COX-2* mRNA expression in non-invasive MCF-7 breast cancer cells by 98.8%, in comparison to benign MCF-10F breast cells. However, western blot analysis showed that COX-2 protein expression was significantly higher in MCF-7 cells by 59%, in comparison to MCF-10F cells. These contradictory results were concordant with observations from other groups (32). Singh-Ranger *et al.* and Zhao *et al.* found an increase of *COX-2* mRNA expression in hormone receptor-positive mammary carcinoma (32, 37). These findings are opposed to the observation that COX-2 protein expression is elevated in hormonereceptor-negative breast cancer (32). *COX-2* mRNA expression is detected in an average of 90% of all breast carcinomas. The difference in mRNA and protein expression levels is probably based on post-transcriptional processing and post-translational alterations. COX-2 may undergo complex modifications to yield the active enzyme (35).

Table I. Summary of the results of immunohistochemical studies of COX-2 expression and their correlation with distinct clinico pathological parameters in breast tissues

Author, year (ref)	N	Tissue COX-2-positive (%)			Clinical and pathological parameter correlates							
		Cancer	DCIS	Normal	Angiogenesis	Hormone-receptor status	HER2	Grading	Age	N+	Extensive tumor	
Hwang <i>et al.</i> , 1998 (76)	44	2/44 (4.5%)	-	-			Not examined					
Koki <i>et al.</i> , 2002 (92)	27	7/17 (42%)	8/10 (80%)	-			Not examined					
Half <i>et al.</i> , 2002 (31)	106	18/42 (43%)	10/16 (63%)	39/48 (81%)	-	No	No	-	-	-	-	-
Denkert <i>et al.</i> , 2002 (93)	221	80/221 (36%)	-	0%	Yes	Yes	-	Yes	No	Yes	Yes	Yes
Costa <i>et al.</i> , 2002 (94)	46	50%	-	-	Yes	No	No	No	No	Yes		
Ristimäki <i>et al.</i> , 2002 (9)	1576	589/1576 (37.4%)	-	-	-	Yes	Yes	Yes	-	Yes	Yes	Yes
Kelly <i>et al.</i> , 2002 (95)	106	90/106 (85%)	-	-	No	No	No	No	No	No	No	No
Davies <i>et al.</i> , 2003 (62)	86	63/86 (79%)	-	-	Yes	No	No	No	No	No	No	No
Lim <i>et al.</i> , 2003 <sup>b</sup> (96)	128	41%	-	-	Yes	-	-	Yes	-	Yes	Yes	Yes
Wulfing <i>et al.</i> , 2003 (97)	192	40.6%	-	-	-	Yes	Yes	Yes	-	-	-	Yes
Boland <i>et al.</i> , 2004 (98)	65	41/65 (63%)	-	-	-	Yes	Yes	-	-	-	-	-
Nassar <i>et al.</i> , 2007 (64)	43	41/43 (95%)	-	-	-	No	No	Yes	-	-	-	Yes
Zhang <i>et al.</i> , 2008 (63)	70	46/70 (65.7%)			Yes	Yes	No	No	No	-	-	No

*Post-transcriptional processing of COX-2 mRNA.* COX-2 mRNA has a very short half-life (38-39). Specific micro RNAs (miRNAs) have been identified which suppress COX-2 protein synthesis. miRNAs are small RNA sequences which do not encode for proteins and regulate gene expression at the mRNA level (40). The gene regulation is enhanced by binding of the miRNAs to the 3' untranslated region (3'UTR) of the mRNA target genes. Either the translation of these target genes is inhibited or they are metabolized by dissection according to the complementarity of the binding sequence and the involved proteins. Partial complementarity results in inhibition of translation, while perfect base pairing leads to degradation of the target mRNA (40-42). Thus transcription may result in adequate mRNA, but translation may possibly be influenced by several factors and the COX-2 protein is then not expressed. For example, interleukin-1 (IL-1) stabilizes COX-2 mRNA, whereas steroids destabilize it (43, 44).

## Role of COX-2 in Tumourigenesis

*Up-regulation of COX-2 expression.* COX-2 protein expression is regulated by transcription and post-transcriptional processes. The COX-2 gene contains multiple transcription binding sites. An example is the cAMP response element (CRE), a binding site for IL-6 and for nuclear factor κB (NFκB) (32). In malignant cells, dysregulated cytokines, oncogenes, growth factors and hormones enhance COX-2 expression (32). In a murine model, high levels of p53, the 'guardian of the genome' are associated with a reduction of the activity of the COX-2 promoter (45).

*COX-2 and carcinogenesis.* The similarity of pathophysiological reactions in inflammation and in cancer is based on several molecular factors: An elevation of cytokines, chemokines and proteases is observed both in malignancies and in inflammation (16). Overexpression of COX-2 in epithelial

Table II. Overview of COX-2 mRNA expression and its correlation with distinct clinico pathological parameters in breast cancer.

Author, year (ref)	N	COX-2-mRNA positive (%)	Clinico pathological correlation with						
			Angiogenesis	Hormone-receptor status	HER2	Grading	Age	N+	Extensive tumour
Kirkpatrick <i>et al.</i> , 2002 (99)	40	40/40 (100%)			Not examined				
Half <i>et al.</i> , 2002 (31)	9	9/9 (100%)			Not examined				
Watanabe <i>et al.</i> , 2003 (33)	7	7/7 (100%)	-	-	-	-	-	-	-
Yoshimura <i>et al.</i> , 2003 (34)	20	10/20 (50%)	-	-	-	-	-	-	-
Singh-Ranger <i>et al.</i> , 2003 (100)	18	18/18 (100%)	Not examined	Yes (PR+)			Not examined		
Zhao <i>et al.</i> , 2003 (101)	30	27/30 (90%)	-	Yes (ER+)	-		Not examined		

carcinomas has been detected in several types of tissue, such as colon, gastric, oesophageal, lung, liver, pancreas, prostate, ovary and breast, and has been associated with carcinogenesis, particularly neoangiogenesis, and tumor progression (5-15). The hypothesis of COX-2-promoted carcinogenesis has been corroborated among others by a transgenic mouse model (46). The data for correlation of COX-2 expression and clinicopathological parameters in breast cancer tissues are controversial, but there is evidence showing a tendency towards a positive correlation with defined parameters of poor prognosis (26, 31). COX-2 apparently promotes the transcription of aromatase and thus promotes enlargement of tumor cells in oestrogen-responsive breast cancer (47). Evidence clearly shows a chemopreventive effect of aspirin and other NSAIDs on colorectal cancer and initial studies report a reduction of breast cancer risk by taking aspirin and ibuprofen (48, 49). A meta-analysis of 14 epidemiological studies indicated that continuous intake of COX inhibitors reduces the risk for breast cancer by up to 24% (50, 51). Tumor cells with elevated COX-2 levels are highly resistant to apoptosis, have increased proliferation, invasion and migration, and even exhibit chemoresistance (35). COX-2 is the key enzyme for prostaglandin synthesis; high COX-2 levels induce high levels of prostaglandins and high levels of prostaglandins have been associated with carcinogenesis. Prostaglandins stimulate cell proliferation and induce mitogenesis of mammary epithelial cells (32). Prostaglandin levels have been demonstrated to be elevated in lesions containing neoplastic cells, e.g. lymphatic and blood vessels, and lymphatic nodes; high PGE<sub>2</sub> levels have also been observed in human breast cancer cell lines, as well as in invasive human breast cancer tissues (52-54). PGE<sub>2</sub> promotes the activity of CYP19, an aromatase gene which enhances local oestrogen production and thus influences tumour growth in hormone dependent breast cancer. COX-2

and CYP19 mRNA levels show a significant correlation (37). High PGE levels enhance COX-2 expression by binding to the PGE receptor in terms of a positive feedback mechanism (32). PGE<sub>2</sub> is one of the most prevalent prostaglandins and acts as a ligand of the G-protein coupled receptors EP<sub>1-4</sub>. The pivotal role of the EP<sub>1</sub> receptor in colon carcinogenesis was demonstrated by receptor knock-out mice and selective EP<sub>1</sub> receptor antagonists (55). The signalling pathway via G<sub>s</sub>/cAMP/protein kinase, which follows the binding of the ligand to the EP<sub>2</sub> receptor, enhances Vascular Endothelial Growth Factor (VEGF) expression, which is associated with tumor neoangiogenesis (56). Increased VEGF expression enhances chronic processes such as angiogenesis in inflammatory processes and is also detectable in invasive tumor cells (56). Prostaglandins directly induce gene expression by ligand binding to nuclear receptors PGI<sub>2</sub>/PGA<sub>2</sub>. The catabolic enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) inactivates the most prevalent PGE<sub>2</sub> and thus constitutes a tumour-suppressing enzyme (57). Low levels of 15-PGDH are associated with factors of poor prognosis, while an increase of 15-PGDH has been observed in the comparatively well differentiated ER-positive breast cancer cell line MCF-7 (57). COX-2 also plays an essential role in the carcinogenesis of intestinal tumours. COX-2 knock-out mice exhibited 86% fewer intestinal polyps (58).

*COX-2 and apoptosis.* Liu *et al.* used a murine model to demonstrate the impact of COX-2 on apoptosis (46) and showed that COX-2 overexpression induces tumorigenesis. Such tumours are characterized by lower expression of pro-apoptotic proteins, BAX and BCL-Xs, two members of the BCL2 protein group, and an increased anti-apoptotic BCL2 protein. Thus COX-2 overexpression is associated with reduced apoptosis (46). Furthermore, mice treated with the

COX-2 inhibitor celecoxib exhibited increased levels of the pro-apoptotic protein Bax and lower levels of Bcl-2 (29). Increased prostaglandin levels are also associated with a rise in cellular cyclic AMP (cAMP) and consequently with reduced apoptosis (32). Furthermore, increased activity of COX-2 reduces the level of arachidonic acid, the substrate of COX-2 in prostaglandin metabolism. Depletion of arachidonic acid is, thus, also associated with a decrease in cellular apoptosis (32).

**COX-2 and neoangiogenesis.** COX-2 expression induces expression of angiogenic factors, *e.g.* VEGF, basic fibroblast growth factor (bFGF), transforming growth factor 1 (TGF-1), platelet-derived growth factor (PDGF) and endothelin (32). On the other hand, the COX-2 inhibitor celecoxib inhibits expression of angiogenic proteins VEGF, Growth Related Oncogene (GRO), IL-6, IL-8, tissue inhibitor of metalloproteinases (TIMP)-1 and TIMP-2 (30). PGE<sub>2</sub> ligand binding at its receptor EP<sub>2</sub> enhances a G s/cAMP/protein kinase, a signal transduction pathway which enhances VEGF expression (59-60). In COX-2 null mice, tumor growth is significantly attenuated and these tumours have reduced vascular density (61).

Davies *et al.* demonstrated a significant correlation between COX-2 expression and the platelet endothelial cell adhesion molecule-1 (PECAM-1, CD31) in breast cancer. In endothelial cells, CD 31 plays a pivotal role in migration and angiogenesis (62). Zhang *et al.* observed that a co-expression of COX-2 and VEGF-C is associated with *lymphangiogenesis carcinomatosa* and a poor survival outcome in breast cancer (63). In poorly differentiated breast cancer cells, the classical pathways of neoangiogenesis can be by-passed. These tumors are supplied by nutritive canals without endothelial cell participation. This phenomenon is called vasculogenic mimicry and is more pronounced in highly invasive breast cancer cell lines with high COX-2 expression levels *in vitro*. Furthermore, celecoxib inhibited vasculogenic mimicry *in vitro* (30).

### COX-2 and Clinicopathological Prognostic Markers

COX-2 expression is associated with factors of poor prognosis, *e.g.* negative hormone receptor status, positive HER2-neu receptor status, high Ki 67 proliferative rate, larger tumor size, high nuclear grading, poor differentiation, vascular invasion, positive lymph nodes, distant metastasis and poor survival outcomes (26, 32, 64). Recently, in the Nurses' Health Study, COX-2 breast cancer expression was associated with higher stage at diagnosis in a patient population of 2,001 women (65).

**COX-2 and hormone receptor status.** COX-2 expression correlates significantly with a negative hormone receptor

status in breast cancer (32). Furthermore elevated PGE<sub>2</sub> levels in human breast cancer cell lines are associated with a negative hormone receptor status (66). The ER metabolism is associated with prostaglandin metabolism. COX-2 expression correlates significantly with mRNA expression of aromatase in breast cancer (67) and furthermore, real-time-PCR analysis demonstrated that COX-2 induces aromatase transcription, whereas COX-2 inhibitors reduce aromatase transcription (47). Increased aromatase activity enhances levels of oestrogen, which induce increased hormone receptor expression (68). Thus, in hormone receptor-positive breast cancer, COX-2 expression enhances oestrogen levels and, consequently, tumor growth. In hormone receptor-positive breast cancer, COX-2 expression correlates with disease progression in endocrine treatment. COX-2 plays a major predicative role for adverse effects of tamoxifen in breast cancer patients (69).

**COX-2 and HER2.** Where specifically investigated, COX-2 expression correlates significantly with positive HER2-neu status in breast cancer (32). The COX-2 inhibitor nimesulide selectively induces apoptosis in HER2 overexpressing breast cancer cells *via* cytochrome c-dependent mechanisms. This effect cannot be observed in HER2-negative breast cancer cell lines (70). Dillon *et al.* observed that HER2 can regulate COX-2 expression through direct transcriptional mechanisms (69).

### COX-2 and Metastasis

COX-2 expression correlates significantly with metastasis in breast cancer (32). In breast cancer cell lines elevated PGE<sub>2</sub> levels are associated with increased metastatic potential (66). Ranger *et al.* analysed archival specimens of human breast cancer (n=29) for COX-2 expression using IHC and obtained clinicopathological data from medical records. Although the patient number was small, these clinical data showed a significant correlation between COX-2 expression and distant metastasis (15). Recently, Kang *et al.* found that the invasive activity of a doxorubicin-resistant MCF-7 cell-line was mediated by COX-2 (71).

### COX-2 and Ductal Carcinoma In Situ (DCIS)

Only few studies reported an analysis of COX-2 expression in DCIS of the breast; however, in comparison to invasive cancer, COX-2 expression was found in a larger proportion of tissues, *e.g.* 67-100%, in comparison to invasive cancer (32). Half *et al.* hypothesized that COX-2 up-regulation is an early event in carcinogenesis and thus is overexpressed in pre-invasive lesions (31). Women with initial DCIS lesions that express COX-2 have a higher risk for developing subsequent invasive cancer in comparison to those with COX-2 negative DCIS (72). These results were corroborated

by meta-analyses (73-74). Compared to invasive breast cancer, COX-2 expression in DCIS correlates with HER2-neu expression and hormone receptor negativity (32).

### COX Suppression as a Therapeutic and Preventive Strategy

*NSAIDs inhibit COX expression.* There are different subtypes which are either COX-2 selective, the so-called coxibs, *e.g.* celecoxib and rofecoxib, or non-selective, *e.g.* acetylsalicylic acid, ibuprofen and indomethacin, which block both subtypes of COX. Selective COX-1 inhibitors play a minor role (75), although a COX-1 overexpression in tumour tissue has been described (76). *In vitro* data showed that COX-1 and COX-2 null cells still have a high PGE<sub>2</sub> production due to the increased transcription of the remaining functional gene (77). Rozic *et al.* demonstrated that selective and nonselective COX-2 inhibitors delayed tumor progression in a COX-2-expressing murine mammary tumor model by inhibiting tumor cell migration, invasiveness and tumour-induced angiogenesis. The inhibitory effects were not entirely prostaglandin dependent; some prostaglandin-independent effects were also noted (5). Epidemiological studies support the hypothesis of breast cancer prevention by NSAID administration. A meta-analysis of 14 epidemiological studies showed a decrease in breast cancer risk by 18% after constant NSAID use (50). Sharpe *et al.* (78) even reported a reduction of breast cancer risk by 24%, while Harris *et al.* observed a reduction by 40% by NSAID intake (78-79). Therapeutic administration of NSAIDs in breast cancer is corroborated by animal experiments. Breast cancer tumor volume in rats was reduced by 32% when celecoxib was administered in comparison to 518% tumour growth without therapy (80). Rats which received celecoxib developed significantly less breast carcinoma after application of a potent carcinogen (7,12-dimethylbenzanthracene) in comparison to the control group (81). In a murine model of breast cancer, celecoxib reduced tumor growth by 58.7% (82). Yoshinaka *et al.* demonstrated tumour reduction, increased apoptosis, reduced DNA synthesis in tumour tissue and reduction of *Vegf* mRNA, *e.g.* a reduction in neoangiogenesis by celecoxib administration in mice (83). Even distant metastasis was reduced by celecoxib in a murine tumor model (29). First therapeutic approaches suggest a combination of COX inhibitors and calcitriol (35-36) because both prostaglandin and calcitriol metabolism influence carcinogenesis and tumour growth. They are linked by various factors and thus a synergistic effect is supposed. The group of Moreno *et al.* already demonstrated growth inhibition of prostate cancer cells by COX-2 inhibitors and calcitriol (84). As COX-2 and estrogen metabolism show synergism, simultaneous COX-2 inhibition and aromatase inhibition represent an interesting therapeutic strategy. The

German Breast Group (GBG) is conducting a multicenter clinical phase III study, the REACT study, which analyses the combination of exemestane and celecoxib in the adjuvant setting of breast cancer. First results have shown a benefit in the metastatic setting of 74%, while more recent results have shown no significant difference (85-88). Another clinical phase II study investigated the combination of celecoxib with capecitabine in the metastatic setting and showed a clinical benefit of 47.5% (89). Brown *et al.* suggested a combination therapy of COX-2 inhibitor and retinoid X receptor-selective retinoid in HER2-neu-positive breast cancer (90). Various other combination therapies with cyclooxygenase-2 inhibitors have been proposed and are currently being investigated. There are several questions that remain unanswered. Recent studies in ovarian cancer suggest that COX-1 overexpression may also play an important role in tumour growth (91), which leads to the question, is non-selective inhibition of COX-1 and COX-2 more effective than selective inhibition? What is the definite role of the different prostaglandin receptors in carcinogenesis and do they have any prognostic value? Therefore, besides the existing encouraging results, further work is required to establish how the COX system can be used as an effective therapeutic approach in the treatment of breast cancer and other solid malignancies.

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