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Advances in Brief

Prognostic Significance of Elevated Cyclooxygenase-2 Expression in Breast Cancer[1]

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Abstract

Cyclooxygenase-2 (Cox-2) expression can induce mammary tumorigenesis in transgenic mice, and selective Cox-2 inhibitors are both chemopreventive and chemotherapeutic in rat models of breast cancer. We analyzed the expression of Cox-2 protein by immunohistochemistry in tissue array specimens of 1576 invasive breast cancers. Moderate to strong (elevated) expression of Cox-2 protein was observed in 37.4% of the tumors, and it was associated with unfavorable distant disease-free survival ($P < 0.0001$). Elevated Cox-2 expression was associated with a large tumor size, a high histological grade, a negative hormone receptor status, a high proliferation rate (identified by Ki-67), high p53 expression, and the presence of *HER-2* oncogene amplification ($P < 0.0001$ for all comparisons), along with axillary node metastases and a ductal type of histology ($P = 0.0001$ and $P = 0.0017$, respectively). Interestingly, association with the unfavorable outcome was especially apparent in the subgroups defined by estrogen receptor positivity, low p53 expression, and no *HER-2* amplification ($P < 0.0001$ for all comparisons). These results indicate that elevated Cox-2 expression is more common in breast cancers with poor prognostic characteristics and is associated with an unfavorable outcome. The present findings support efforts to initiate clinical trials on the efficacy of Cox-2 inhibitors in adjuvant treatment of breast cancer.

Introduction

Epidemiological studies indicate that the use of NSAIDs[4] is associated with a reduced risk of malignancies in the digestive tract (1). The association of NSAID use with the incidence of nongastrointestinal malignancies is less clear, but a recent meta-analysis suggests that the use of NSAIDs may reduce the risk of breast cancer (2). The best-known target of NSAIDs is the Cox enzyme. Two isoforms of Cox are known, of which Cox-1 is expressed in a constitutive manner, and its role has been connected to physiological functions, such as cytoprotection of the stomach and control of platelet aggregation. In contrast, expression of Cox-2 is not detectable in most healthy tissues but can be induced in response to cell activation by proinflammatory cytokines, growth factors, and tumor promoters, and its role has been connected to inflammation and carcinogenesis (1, 3). Expression of the Cox-2 isoform (but not that of Cox-1) is elevated in a variety of human malignancies and in premalignant lesions (4). Functionally, Cox-2-derived prostanoids have been shown to promote angiogenesis, induce invasion, and increase metastasis (1, 3). Because of its high expression in neoplasias, Cox-2 constitutes a relevant target in chemoprevention of cancer. Indeed, selective Cox-2 inhibitors suppress carcinogenesis in rodent models, and genetic disruption of *Cox-2* inhibited polyp formation in *Apc* $^{\Delta 716}$-knockout mice, which are a model for familial adenomatous polyposis (5). Furthermore, a selective Cox-2 inhibitor was shown recently to reduce the polyp burden in patients with familial adenomatous polyposis (6). Recent reports suggest that Cox-2 may be directly involved with mammary carcinogenesis, because Cox-2-selective inhibitors suppressed tumorigenesis in rat models of breast cancer (reviewed in Ref. 3), and because expression of Cox-2 as such was sufficient for formation of breast tumors in transgenic mice (7). In breast cancer patients, expression of Cox-2 mRNA and protein is elevated (8–11), but the clinical relevance of this finding is unknown. The aim of this study was to assess whether expression of Cox-2 protein is associated with clinicopathological parameters and clinical outcome in a large population-based cohort of invasive breast cancer patients as analyzed by immunohistochemistry.

Materials and Methods

Patients. Five well-defined geographical regions, comprising approximately 50% of the Finnish population, were selected for the study. Using the files of the nationwide Finnish Cancer Registry, we identified all women diagnosed with breast cancer in 1991 and 1992. Using structured data collection forms, the clinical data of 50 characteristics were extracted from the hospital records (for details see Ref. 12). A total of 2842 patients (93% of all breast cancer patients) with sufficient clinical data available were entered into the FinProg Breast Cancer Database, of whom 1984 were included in the study; patients with *in situ* carcinoma ($n = 201$), distant metastasis at the time of diagnosis ($n = 133$), synchronous or metachronous bilateral breast cancer ($n = 281$), malignancy other than breast cancer in history except for basal cell carcinoma or cervical *in situ* carcinoma ($n = 201$), and women who did not undergo breast surgery ($n = 42$) were excluded. Fifty-seven percent of patients older than 50 years received adjuvant antiestrogen therapy, and 37% of patients younger than 50 received adjuvant chemotherapy. The median length of follow-up of patients alive at the end of follow-up was 6.8 years (range, 5.1–7.8).

Preparation of Tumor Tissue Arrays and Immunohistochemistry. Routinely fixed paraffin-embedded tumor samples were extracted from the files of pathology laboratories, and histopathologically representative tumor regions were used for preparation of tumor tissue array blocks (13). From the 1728 tumor samples available, 19 tissue array blocks were prepared, each containing 50–144 tumor sample cores (diameter 0.6 mm). Sections of 5 μm were cut and processed for immunohistochemistry. Specimens were deparaffinized, antigen was retrieved using a microwave oven, and immunostaining was performed using a Cox-2-specific antihuman mouse monoclonal antibody (2.5 μg/ml; 160112; Cayman Chemical Co., Ann Arbor, MI) as described previously (14). Suitability of the antibody for immunohistochemistry has been reported recently (15). Specificity of the antibody was confirmed by staining one tumor tissue array slide with and without preadsorption of the primary antibody with a human Cox-2 control peptide (10 μg/ml; Cayman Chemical). Immunostaining for ER, PgR, Ki-67, and p53 was carried out using established procedures (16). *HER-2* gene amplification was assessed using chromogenic *in situ* hybridization according to the method of Tanner *et al.* (17).

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[4] The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; Cox, cyclooxygenase; CI, confidence interval; DDFS, distant disease-free survival; ER, estrogen receptor; PgR, progesterone receptor.

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Evaluation of Cox-2 Immunostaining. Cox-2 immunohistochemical staining was scored independently and in a blinded manner by two investigators (A. R. and A. S.) from 1728 tissue array cores, of which 152 (8.8%) either detached or did not contain tumor cells. The following scoring criteria of the tumor cells were agreed upon before the analysis: 0, no staining; 1+, weak diffuse cytoplasmic staining (may contain stronger intensity in less than 10% of the cancer cells); 2+, moderate to strong granular cytoplasmic staining in 10–90% of the cancer cells; 3+, over 90% of the tumor cells stained with strong intensity.

Statistical Analysis. The χ^2 test was used to test for associations between factors and the odds ratio to examine the strength of the relationships. The agreement between the two pathologists in the scoring of Cox-2 expression levels was estimated by percent-agreement and κ-statistics. Life-tables were calculated according to the Kaplan-Meier method. DDFS was calculated from the date of the diagnosis to the occurrence of metastases outside the locoregional area or death from breast cancer, whichever came first. Survival curves were compared with the log-rank test. Multivariate survival analyses were performed with the Cox proportional hazards model, entering the following covariates: Cox-2 expression (score 0–1 *versus* 2–3), age (<50 *versus* ≥50 years), the number of metastatic lymph nodes (continuous), tumor size in centimeters (continuous), histological grade (well differentiated *versus* moderately to poorly differentiated), histological type (nonductal *versus* ductal), ER (positive *versus* negative), PgR status (positive *versus* negative), *HER-2* amplification (negative *versus* positive), Ki-67 expression (<20% *versus* ≥20% positive tumor cells), and p53 expression (<20% *versus* ≥20% positive tumor cells). Cox regression was done using a backward stepwise selection of variables, and a P of 0.05 was adopted as the limit for inclusion of a covariate. The assumption of proportional hazards was ascertained with complementary log plots.

Results

Cox-2 Immunohistochemistry of the Breast Cancer Specimens. Immunoreactivity of Cox-2 was evaluated in 1576 invasive breast carcinomas, of which 8.4% were negative and 54.2% weakly, 32.4% moderately, and 5.0% strongly positive. Elevated expression of Cox-2 protein was defined as moderate (2+) or strong (3+) cytoplasmic granular Cox-2 immunoreactivity, which was observed in 37.4% of the tumors. Moderate to strong Cox-2 immunoreactivity localized exclusively to the cytoplasm of the tumor cells, whereas the stroma was either negative or weakly positive (Fig. 1). The percent-agreement between the two independent investigators in allocation of the tumors into these two categories was 85% (κ-coefficient 0.69). All specimens with discordant scores were reevaluated by the two investigators using a multiheaded microscope, and the consensus score was used for further analyses. One tumor tissue array slide was stained with and without preincubation with the antigenic peptide, and all cancer cell positivity was blocked by this control procedure.

Association of Cox-2 with Clinicopathological Parameters. Elevated expression of Cox-2 was significantly more frequent in ductal carcinomas (39.9%) as compared with lobular (29.5%) or special (30.8%; tubular, medullary, mucinous, and papillary) histological types ($P = 0.0017$; Table 1). Within the subgroup of ductal tumors, Cox-2 was associated with high histological grade ($P < 0.0001$). Elevated Cox-2 expression was more common in tumors with large size, negative hormone receptor status, high Ki-67 expression, high p53 expression, and *HER-2* amplification ($P < 0.0001$ for each comparison). A significant association was also found with the presence of axillary lymph node metastases ($P = 0.0001$). No significant association was found between Cox-2 and age at diagnosis when 50 was used as the cutoff value.

Association of Cox-2 with Distant Disease-free Survival. Elevated Cox-2 expression was associated with decreased DDFS among the 1576 breast cancer patients. This was evident when the Cox-2 high category (scores 2–3) was compared with the Cox-2 low category (scores 0–1), or when each score (0–3) was analyzed separately (Fig. 2). Five-year DDFS in Cox-2 low category was 83% (95% CI, 81–86) and in Cox-2 high category 73% (95% CI, 70–77) ($P < 0.0001$). Interestingly, we observed that the prognostic impact of Cox-2 was not similar in different subgroups of the patients. Elevated Cox-2 expression predicted poorer survival in patients with ER-positive tumors ($P < 0.0001$), but not significantly in the hormone receptor-negative ones (Table 2). Significant differences were observed also when the patient series was split according to p53 expression and *HER-2* amplification, in which the prognostic impact of Cox-2 was significant only in the subgroups with no abnormalities of these genes ($P < 0.0001$ for both). Cox-2 also had significant prognostic value in tumors with a low proliferation rate (identified by Ki-67; $P = 0.001$), whereas the association was not significant in rapidly proliferating tumors. However, the percentage of difference in 5-year DDFS between patients with low and high Cox-2 expression was more marked in axillary node-positive disease when compared with negative-node disease. (Table 2).

Multivariate Analysis. Multivariate survival analysis was performed to evaluate the independence of Cox-2 expression as a prognostic factor. In this analysis large tumor size (RR = 1.26; 95% CI, 1.15–1.37; $P < 0.0001$), number of axillary node metastases (1.14; 95% CI, 1.10–1.18; $P < 0.0001$), PgR negativity (1.8; 1.30–2.55; $P = 0.0005$), moderate to poor histological differentiation grade (2.84; 1.48–5.47; $P = 0.0017$), and *HER-2* amplification (1.46; 1.05–2.04; $P = 0.0233$) were recognized as independent prognostic factors, whereas age, histological type, or expression of Cox-2, ER, p53, or Ki-67 did not add significant independent prognostic information.

Discussion

Our present results provide, for the first time, evidence for Cox-2 protein expression in a large series of breast carcinomas ($n = 1576$). According to our data, elevated expression of Cox-2 protein was more common in the breast cancers that displayed markers for poor prognosis, and it correlated significantly with reduced survival. We de-

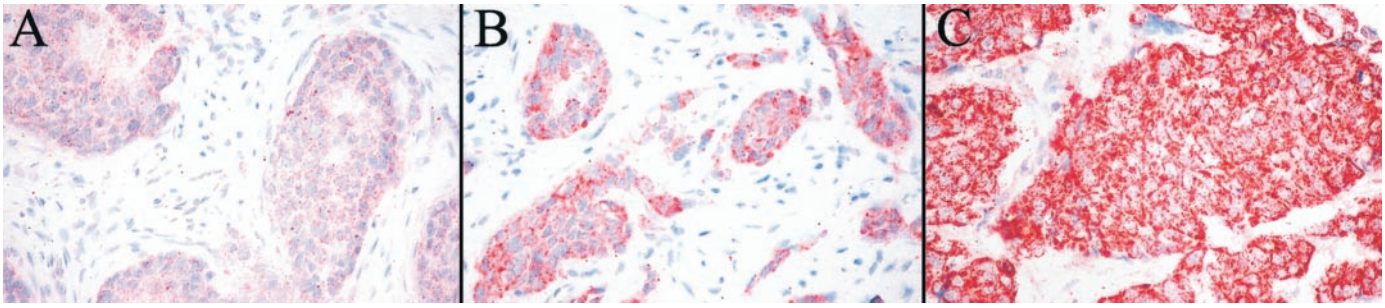

Fig. 1. Representative examples of Cox-2 immunohistochemistry in the breast tumor tissue array specimens. Weak (*A*; score 1), moderate (*B*; score 2), and strong (*C*; score 3) immunopositivity was evident in the neoplastic cells, whereas the stroma was negative.

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Table 1 *Association of elevated Cox-2 immunopositivity (score 2–3) with clinicopathological parameters*

Clinicopathological parameter	Cox-2 staining (positive/total)	Cox-2 positive (%)	P^a (odds ratio)
Age at diagnosis (yr)			
<50	147/418	35.2	NS;[b] 0.167
≥50	442/1158	38.2	(0.88; 0.69–1.12)
Tumor size (cm)			
≤2 cm	288/894	32.2	<0.0001
>2 cm	276/601	45.9	(0.56; 0.45–0.70)
Axillary node status			
Negative	331/983	33.7	=0.0001
Positive	231/530	43.6	(0.66; 0.53–0.82)
Histologic grade[c]			
I	47/183	25.7	<0.0001
II	181/492	36.8	
III	148/284	52.1	
Histologic type			
Ductal	461/1155	39.9	=0.0017
Lobular	74/251	29.5	
Special	48/156	30.8	
ER			
Negative	234/447	52.3	<0.0001
Positive	330/988	33.4	(0.46; 0.36–0.58)
PgR			
Negative	314/643	48.8	<0.0001
Positive	249/786	31.7	(0.49; 0.39–0.61)
Tumor proliferation			
Ki-67 <20%	277/840	33.0	<0.0001
Ki-67 ≥20%	264/489	54.0	(0.42; 0.33–0.53)
p53 expression			
Negative/Low	391/1070	36.5	<0.0001
High	143/242	59.1	(0.40; 0.30–0.54)
HER-2 oncogene amplification			
Negative	425/1157	36.7	<0.0001
Positive	132/262	50.4	(0.57; 0.43–0.76)

[a] χ^2 test.
[b] NS, not significant.
[c] Ductal type only.

Table 2 *Five-year DDFS according to Cox-2 expression level*

Clinicopathological parameter	Cox-2 score	*n* (%)	DDFS (95% CI)	P^a
Age <50 yr	0–1	271 (64.8)	79 (74–84)	NS;[b] 0.058
	2–3	147 (35.2)	71 (64–79)	
Age ≥50 yr	0–1	716 (61.8)	85 (82–88)	<0.0001
	2–3	442 (38.2)	74 (69–78)	
Size ≤2 cm	0–1	606 (67.8)	89 (86–91)	0.013
	2–3	288 (32.2)	83 (79–88)	
Size >2 cm	0–1	325 (54.1)	72 (67–77)	NS; 0.052
	2–3	276 (45.9)	64 (58–70)	
Node negative	0–1	652 (66.3)	90 (88–92)	0.011
	2–3	331 (33.7)	86 (82–90)	
Node positive	0–1	299 (56.4)	69 (64–74)	0.006
	2–3	231 (43.6)	56 (49–63)	
Grade 1[c]	0–1	136 (74.3)	96 (93–100)	0.037
	2–3	47 (25.7)	91 (82–100)	
Grade 2[c]	0–1	311 (63.2)	78 (74–83)	0.009
	2–3	181 (36.8)	70 (63–77)	
Grade 3[c]	0–1	136 (47.9)	69 (61–77)	NS; 0.543
	2–3	148 (52.1)	64 (55–72)	
Ductal	0–1	694 (60.1)	81 (78–84)	<0.0001
	2–3	461 (39.9)	70 (66–75)	
Lobular	0–1	177 (70.5)	87 (82–92)	NS; 0.232
	2–3	74 (29.5)	81 (71–91)	
Special	0–1	108 (69.2)	94 (89–99)	NS; 0.396
	2–3	48 (30.8)	91 (83–100)	
ER positive	0–1	658 (66.6)	86 (84–89)	<0.0001
	2–3	330 (33.4)	76 (72–81)	
ER negative	0–1	213 (47.7)	70 (64–77)	NS; 0.396
	2–3	234 (52.3)	68 (62–74)	
PgR positive	0–1	537 (68.3)	88 (86–91)	0.002
	2–3	249 (31.7)	80 (74–85)	
PgR negative	0–1	329 (51.2)	73 (68–78)	NS; 0.071
	2–3	314 (48.8)	67 (62–73)	
Ki-67 <20%	0–1	563 (67.0)	87 (84–90)	0.001
	2–3	277 (33.0)	77 (72–82)	
Ki-67 ≥20%	0–1	225 (46.0)	71 (64–77)	NS; 0.097
	2–3	264 (54.0)	67 (61–73)	
p53 negative/low	0–1	679 (63.5)	85 (82–88)	<0.0001
	2–3	391 (36.5)	74 (70–79)	
p53 high	0–1	99 (40.9)	64 (54–74)	NS; 0.842
	2–3	143 (59.1)	68 (60–76)	
HER-2 negative	0–1	732 (63.3)	86 (84–89)	<0.0001
	2–3	425 (36.7)	77 (73–81)	
HER-2 positive	0–1	130 (49.6)	63 (54–71)	NS; 0.729
	2–3	132 (50.4)	59 (50–68)	

[a] Log-rank test or log-rank test for a trend.
[b] NS, not significant.
[c] Ductal type only.

tected elevated levels of Cox-2 protein expression in 37.4% of the carcinomas. Cox-2 mRNA and protein have been reported previously to be expressed in breast cancer specimens (8–11), but the small number of tumors studied and the different methods and cutoff values used make the comparison of these data with our results difficult. In our study, strong Cox-2 expression localized exclusively to the neoplastic cells, whereas the stroma was either negative or weakly positive. In addition, previously published data indicate that Cox-2 expression is exclusively a feature of malignant but not benign epithelium of the breast (8, 9, 11). In contrast, the expression of Cox-1 protein was not elevated in breast cancer cells when compared with their nonmalignant counterparts (11).

In our series, Cox-2 positivity correlated with several parameters that characterize aggressive types of breast cancer, such as large tumor size, presence of axillary node metastases, high histological grade, negative hormone receptor status, high proliferation rate, high p53 expression, and *HER-2* amplification. Consistent with our data, Cox-2 expression is associated with advanced tumor stage, poor differentiation grade, and reduced survival also in gastrointestinal adenocarcinomas (4). The mechanism by which Cox-2 is up-regulated in breast cancers is unknown, but one possibility is that cancer cells become intrinsically more active in expressing Cox-2 than do the nonneoplastic cells. To this end, both inactivation of tumor suppressor genes, such as *p53*, and activation of oncogenes, such as *HER-2*, have been implicated in induction of Cox-2 expression (reviewed in Ref. 3). Our results support this hypothesis, because elevated Cox-2 expression was significantly more common in tumors with high expression of p53 (a marker for inactivation and/or mutation of *p53*) or with amplification of the *HER-2* oncogene. However, because elevated Cox-2 expression was not restricted to p53- and HER-2-positive tumors, several other factors (such as activated Ras, overexpressed Src, and Wnt- or epidermal growth factor receptor-pathway) are likely

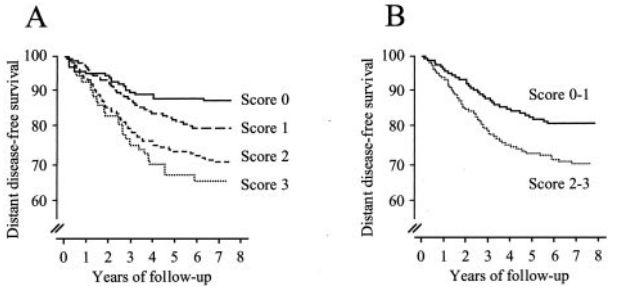

Fig. 2. DDFS of 1576 breast cancer patients according to Cox-2 protein expression. *A*, DDFS of patients with no Cox-2 expression (score 0; $n = 133$) or with weak (score 1; $n = 854$), moderate (score 2; $n = 511$), or strong (score 3; $n = 78$) Cox-2 expression. Elevated expression of Cox-2 protein correlated with reduced survival ($P < 0.0001$; log-rank test for trend). *B*, Cox-2 expression grouped as immunostaining scores 0–1 (Cox-2 low; 987 patients) and scores 2–3 (Cox-2 high; 589 patients; $P < 0.0001$; log-rank test).

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to be responsible for elevated Cox-2 expression as well (3). To this end, it is interesting to note that the antineoplastic effect of inhibitors of both HER-2 and epidermal growth factor receptor is enhanced by combining them with Cox inhibitors (18, 19). Our results showing a high frequency of Cox-2 overexpression in tumors with amplification of *HER-2* oncogene further necessitate studies defining the role of Cox-2 inhibitors as an enhancer of anti-HER-2 therapy in experimental chemotherapeutic models of breast cancer.

Our main finding is that elevated levels of Cox-2 expression are associated with decreased survival in patients with breast cancer. Interestingly, the prognostic value of Cox-2 expression tends to be more marked in certain subgroups of patients, *e.g.*, in cancers with ER positivity, a normal level of p53 expression, and no amplification of the *HER-2* oncogene. This may indicate that the procarcinogenic effect of Cox-2 is not evenly distributed in breast cancer. However, Cox-2 expression was associated with significantly poorer survival in both node-negative and node-positive cancers. This may reflect the ability of Cox-2 to induce metastasis; for example, by inducing production and activation of matrix metalloproteinases (1, 3). The fact that elevated expression of Cox-2 is associated with poor survival in ER-positive tumors is of particular interest. Because Cox-2-derived prostanoids have been implicated in the enhancement of stromal cell aromatase expression (10, 20), it is possible that elevated Cox-2 expression in ER-positive cancers could enhance a growth-promoting microenvironment for the tumor cells by inducing estrogen production via the aromatase pathway in the stromal cells. Thus, our results provide a basis to study the predictive value of Cox-2 expression in the context of clinical trials aimed at assessing the efficacy of novel aromatase inhibitors *versus* the classical antiestrogen tamoxifen. Although no conclusions with regard to treatment can be drawn from the association between Cox-2 expression and poor outcome, the present findings support efforts to initiate clinical trials on the efficacy of Cox-2 inhibitors in adjuvant treatment of breast cancer.

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Ari Ristimäki, Anna Sivula, Johan Lundin, et al.

Cancer Res 2002;62:632-635.

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