ORIGINAL ARTICLE

Expression of cyclooxygenase-2 in colonic polyps

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KEY WORDS

carcinogenesis, colonic polyps, cyclooxygenase-2, immunohistochemistry

ABSTRACT

INTRODUCTION Limited data is available regarding the relationships between cyclooxygenase-2 (COX-2) and colorectal cancer formation.

OBJECTIVES The aim of the study was to investigate cyclooxygenase-2 (COX-2) expression in histologically diverse colonic polyps, to determine the association between the expression of this enzyme and selected pathological and clinical characteristics of polyps, and to establish the location of cells with high COX-2 expression within the polyp.

PATIENTS AND METHODS We examined 212 colonic polyps from 175 patients. Immunohistochemical staining with monoclonal anti-COX-2 antibodies was performed

RESULTS Statistically significant differences associated with high COX-2 expression were found: in adenomas vs. other polyps ($P < 0.001$), in adenomas with high-grade dysplasia ($P < 0.000\,001$), and in polyps of the cecum ($P < 0.02$). Statistically significant differences in COX-2 were also associated with polyp size ($P < 0.000\,001$). Cells with high COX-2 expression were usually located in the epithelial layer ($P = 0.01$). No significant associations were found between high COX-2 expression and the age and sex of patients or the total number of polyps.

CONCLUSIONS We demonstrated that high COX-2 expression is associated with typical risk factors for malignant transformation of colonic polyps. The results suggest the possible role of COX-2 in the early stages of colon carcinogenesis.

INTRODUCTION According to the most recent epidemiological reports, colorectal cancer (CRC) is the second most common cause of death among patients with malignant tumors in Poland, with the morbidity rate of 15 to 25 new cases per 100,000 individuals per year.[1] More than 90% of adenocarcinomas develop from the preexistent, histologically benign adenomatous polyps, and only a few develop *de novo* from flat lesions present in the colon wall.[2] The generally recognized risk factors for developing colorectal cancer include: polyp size >10 mm, adenoma with villous features, high-grade epithelial dysplasia, and the total number of polyps detected during colonoscopy.[2]

Unfortunately, little is known about the biological processes involved in the malignant transformation of adenoma into carcinoma. Eicosanoids are chemical substances derived from arachidonic acid. They are present in almost all human cells and bodily fluids. The family of eicosanoids includes prostaglandins, prostacyclines, thromboxanes, leukotrienes, and lipoxins. Their synthesis requires 2 enzymatic pathways: cyclooxygenase (COX) and lipoxygenase.[3] COX is an enzyme responsible for the synthesis of prostaglandins, prostacyclines, and thromboxanes, which, in turn, are responsible for vasodilatation and vasoconstriction, platelet aggregation, fever reaction, and pain sensation.[4] There are 2 known COX isoforms: COX-1 and COX-2.

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TABLE 1 Clinical data and pathology of investigated polyps

Parameter	All polyps (%)	Adenomas (%)
age, y		
<60	94 (44)	77 (42)
≥60	118 (56)	106 (58)
type of polyp		
hyperplastic	25 (12)	0
adenoma	187 (88)	0
type of adenoma		
tubular	0	54 (29)
tubulovillous	0	48 (26)
villous	0	12 (7)
serrated	0	69 (38)
intramucosal adenocarcinoma	0	4 (2)
degree of dysplasia		
low	0	141 (75)
high	0	46 (25)
polyp size, mm		
<10	132 (62)	109 (60)
≥10	80 (38)	74 (40)
location within the colon		
proximal part[a]	65 (31)	56 (31)
cecum	13 (6)	12 (7)
ascending colon	25 (12)	22 (12)
transverse colon	27 (13)	22 (12)
distal part	147 (69)	127 (69)
descending colon	18 (9)	15 (8)
sigmoid colon	75 (35)	68 (37)
rectum	54 (25)	44 (24)
number of polyps detected by colonoscopy		
1	80 (38)	79 (43)
2–5	94 (44)	83 (45)
6–10	23 (11)	11 (6)
>10	15 (7)	10 (6)

a with relation to the splenic flexure

There are conflicting reports concerning the expression of COX-2 in colorectal polyps and carcinomas. The reported results depend on the degree of histological differentiation, site of the carcinoma, size and number of polyps, as well as histological type.[5-15]

The protective effect of nonselective COX-1 and COX-2 inhibitors in colorectal carcinogenesis has been known for a long time. A lower risk of developing CRC and experiencing a relapse after a radical treatment has been proved in patients undergoing a long-term treatment with acetylsalicylic acid.[16,17] Such therapeutic approach is known as chemoprevention.

There are limited data on the enzymes involved in the metabolism of eicosanoids and the role of these enzymes in colorectal adenomas and carcinogenesis. The results of the available studies are often conflicting, and there are no data on the expression of COX-1 and COX-2 in hyperplastic polyps.

The aim of our study was to analyze the level of COX-2 expression in colorectal polyps of several histological types. We investigated the association between the level of COX-2 expression and such parameters as size, histological type, the degree of dysplasia, location of the polyp, total number of colonic polyps, as well as the age and sex of patients after polypectomy. We also analyzed the distribution of COX-2-positive cells within the polyp.

PATIENTS AND METHODS

Tissue specimens

We analyzed 212 colorectal polyps resected from 175 patients. We obtained 95 polyps (45%) from 84 women (aged 30–81 years; mean age 61.5 ±11.3) and 117 (55%) from 91 men (aged 38–85 years; mean age 63.4 ±10.6). We excluded polyps that were resected from patients diagnosed with inflammatory bowel disease and polyposis syndrome. Similarly, we excluded polyps from patients treated with nonsteroidal anti-inflammatory drugs and/or corticosteroids, as well as from patients whose first- or second-degree relatives had been diagnosed with colorectal cancer. The characteristics of patients are presented in TABLE 1.

Immunohistochemistry

Two sets of tissue sections were cut from the paraffin-embedded tissue blocks and mounted on slides. The sections were deparaffinized overnight in 68°C, rinsed with xylene for 40 minutes in the same temperature, and dehydrated through graded alcohols. Antigen retrieval was performed by immersing the sections 3 times for 7 minutes in boiling citrate buffer (pH 6.0), after which the sections were rinsed in phosphate buffer saline (PBS) (pH 7.4). Endogenous peroxidase was blocked by incubation with peroxidase blocking reagent (DAKO Cytomation, S2001) and rinsed in PBS. Incubation with primary antibody (mouse anti-COX-2 monoclonal antibody, Novocastra, diluted 1:25 in Antibody Diluent, S0809, DAKO, United Kingdom) was conducted overnight (~18 h) in room temperature. After incubation, the sections were rinsed in PBS, the secondary antibody was applied (Universal LSAB+ Kit/HRP, K0690, DAKO), and the sections were rinsed again. Then, chromogene was applied (AEC+ High-sensitivity Substrate Chromogene, K3469, DAKO). The sections were rinsed in double-distilled water and counterstained with the Mayer's hematoxylin. Each section was then mounted in the Faramount Aqueous Mounting Medium (S3025, DAKO). Control sections were always included with each set of stained slides.

Microscopic evaluation of stained sections

Stained sections were analyzed using a light microscope, OLYMPUS BX41. Evaluation was performed simultaneously by 2 independent investigators, who analyzed the same optical field using 2 independent visual channels. The analysis included the overall percentage of COX-2-positive cells as well as the intensity of chromogene staining of these cells. Additionally, the distribution of

positive cells was investigated. Expression of COX-2 was classified using the point scale proposed by Soslow et al.,[7] which we modified to maximize the objectivity of our analysis. Modification consisted in dividing each visual field into 4 parts and analyzing each part separately. The point values for each field were then added and averaged. Each polyp sample was analyzed as follows: the areas of highest degree of intraepithelial dysplasia (neoplasia) were selected (magnification × 50–100), and within these, the areas of the highest staining intensity were selected for further analysis (magnification × 400). Such selected fields were then subdivided into 4 quadrants; each quadrant was assessed (as compared with the control) in relation to the intensity of staining: 0 to 3 points ("intensity score": 0 – no staining, 1 – weak, 2 – moderate, 3 – strong) as well as the percentage of positive cells: 0 to 4 points ("quantity score": 0 – <1%, 1 – 1%–25%, 2 – 26%–50%, 3 – 51%–75%, 4 – 76%–100%). Such procedure allowed to obtain 8 scores for each section. The scores were then averaged into one score. The "intensity score" (0–3 points) and the "quantity score" (0–4 points) were multiplied by each other according to the immunohistochemical score system developed by Soslow and based on the German ImmunoReactive Score. The final scores ranged from 0 to 12 and reflected the overall expression of the enzyme within the tissue: 0 to 4 points indicated lack of or weak expression (negative or questionable result), while the score of 5 points or higher indicated an unequivocally positive result (high expression of the enzyme). Finally, the site of the highest expression of COX-2 was determined: 1 – expression only in the epithelium, 2 – expression only in the stroma, 3 – expression observed in both areas.

Statistical analysis Statistical analysis was performed using the STATISTICA 6.0. software. The Pearson's χ^2 and Fischer tests were used to analyze the association between COX-2 expression and selected parameters of the polyps. The nonparametric Mann-Whitney test was used to analyze the association between the size of the polyp and the expression of the enzyme. $P < 0.05$ was considered statistically significant.

RESULTS High COX-2 expression was detected in 115 polyps (54%), while low or lack of expression in 97 (46%). We observed statistically significant differences in COX-2 expression with regard to such parameters as histological structure, the degree of epithelial dysplasia, size and location of the polyps, and distribution of COX-2-positive cells within the polyp.

Histology of the polyps High expression of COX-2 was observed in 105 adenomas (57%), 4 adenocarcinomas (100%), and 6 hyperplastic polyps (24%). Statistically significant differences in COX-2 expression were noted between adenomas and hyperplastic polyps ($P < 0.001$). Twelve villous (100%), 36 tubulovillous (75%), 24 tubular (44%), and 33 serrated adenomas (48%) were characterized as highly positive for COX-2. There were statistically significant differences in COX-2 expression in villous adenomas as compared with tubular and serrated adenomas and hyperplastic polyps ($P < 0.0005$, $P < 0.0008$, $P = 0.00\,001$, respectively). Similarly, COX-2 expression differed significantly in tubulovillous adenomas as compared with tubular and serrated adenomas and hyperplastic polyps ($P < 0.002$, $P = 0.003$, $P = 0.00\,003$, respectively). Finally, statistically significant differences were detected between high expression of COX-2 in serrated adenomas as compared with hyperplastic polyps ($P < 0.04$). The other observed differences did not reach statistically significant levels.

Degree of epithelial dysplasia High COX-2 expression was detected in 42 polyps (91%) with high-grade dysplasia, in 67 polyps (48%) with low-grade dysplasia, and in 6 polyps (24%) without dysplasia. Statistically significant differences were observed between high COX-2 expression in adenomas with high-grade dysplasia as compared with adenomas without dysplasia ($P < 0.000\,001$), as well as in adenomas with low-grade dysplasia as compared with adenomas without dysplasia ($P < 0.000\,001$). Similar level of statistical significance was noted when high COX-2 expression in adenomas with high-grade dysplasia was compared with adenomas with low-grade dysplasia ($P < 0.000\,001$); in 4 cases, adrenocarcinomas were analyzed together with adenomas with high-grade dysplasia. The other observed differences did not reach statistically significant levels. Examples of the various levels of COX-2 expression depending on the type of the polyp and the degree of dysplasia are shown in FIGURES 1 to 5.

Polyp size High COX-2 expression was observed in 87 polyps (76%) larger than 6 mm, including 82 adenomas (76%), and in 28 polyps (29%) smaller than 6 mm, including 23 adenomas (31%). Similarly, high COX-2 expression was detected in 66 polyps (83%) equal or larger than 10 mm, including 61 adenomas (82%), and in 49 polyps (37%) smaller than 10 mm, including 44 adenomas (40%). Statistical analysis of COX-2 expression performed for both polyp sizes (6 and 10 mm), in a group of all polyps and a subgroup of adenomas, revealed that all differences were statistically significant ($P < 0.000\,001$). The association between polyp size and COX-2 expression was additionally analyzed using the Mann-Whitney nonparametric test, which confirmed the statistical significance of the above differences ($P = 4.4 \times 10^{-14}$). There was also a clear positive correlation between high COX-2 expression and polyp size ($P = 4.5 \times 10^{-16}$; R = 0.52).

Location of the polyp High expression of COX-2 was detected in 12 polyps (92%), including 11 adenomas resected from the cecum (92%); in 9 polyps

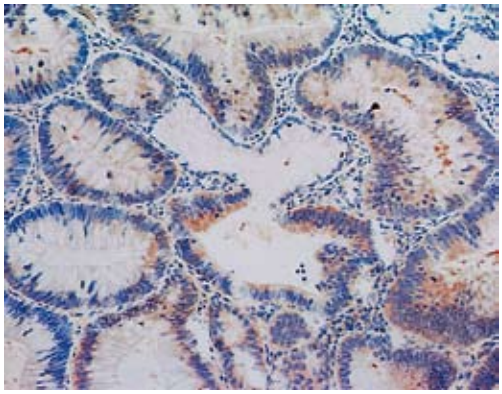

FIGURE 1 Serrated adenoma characterized by moderate level of epithelial dysplasia. Red cytoplasmic staining reflects the presence of COX-2 within epithelial cells. Tissue cross-section was photographed at the magnification of ×400.

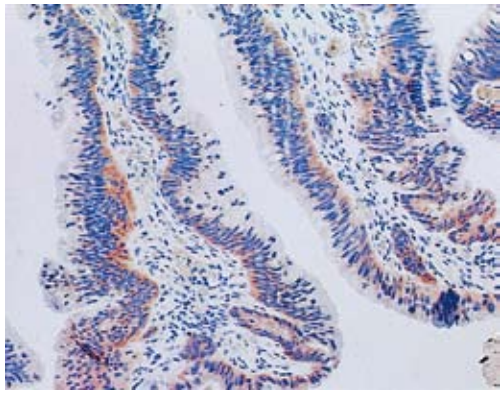

FIGURE 2 Villous adenoma characterized by moderate level of epithelial dysplasia. Red cytoplasmic staining reflects the presence of COX-2 within epithelial cells. Tissue longitudinal section was photographed at the magnification of ×400.

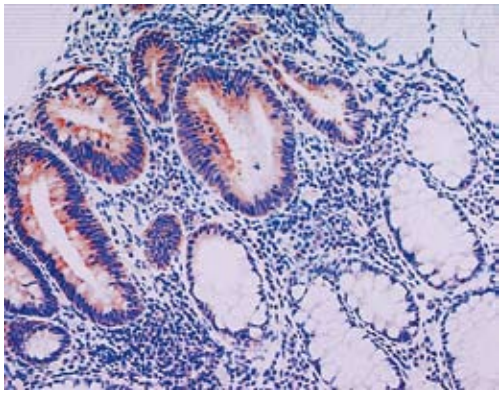

FIGURE 3 Tubular adenoma characterized by low degree of epithelial dysplasia. Red cytoplasmic staining reflects the presence of COX-2 within epithelial cells. Neighboring tubules without dysplastic features are negative for COX-2. Tissue cross-section was photographed at the magnification of ×400.

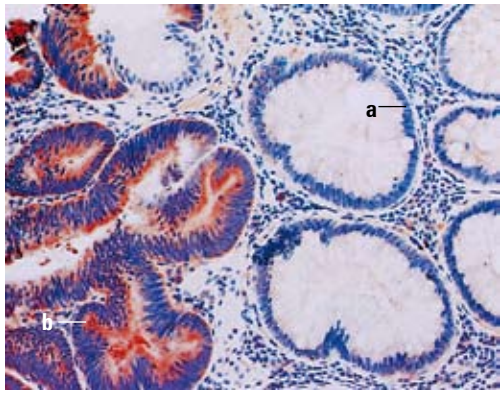

FIGURE 4 Varying expression of COX-2 depending on the degree of epithelial dysplasia; **a** high degree of dysplasia is accompanied by high COX-2 expression; **b** low degree of dysplasia is characterized by low or no COX-2 expression. Red cytoplasmic staining reflects presence of COX-2 within epithelial cells. Tissue cross-section was photographed at the magnification of ×400.

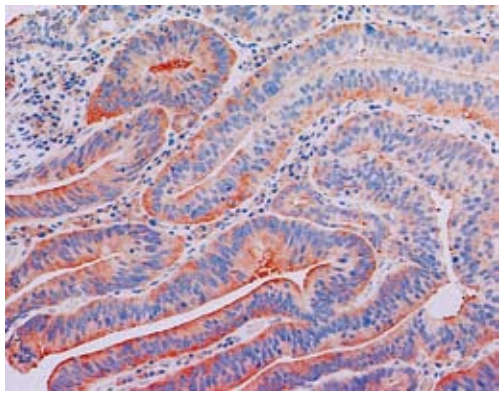

FIGURE 5 Villous adenoma characterized by high degree of epithelial dysplasia. Note higher numbers of strongly positive COX-2 cells as compared to FIGURE 2. Red cytoplasmic staining reflects the presence of COX-2 within epithelial cells. Tissue longitudinal section was photographed at the magnification of ×400.

(36%), including 8 adenomas (36%) resected from the ascending colon; in 13 polyps (48%), including 13 adenomas (59%) from the transverse colon; in 6 polyps (33%), including 3 adenomas (20%) from the descending colon; in 44 polyps (59%), including 42 adenomas (62%) resected from the sigmoid colon; and in 31 polyps (57%), including 28 adenomas (64%) resected from the rectum. Statistically significant differences were observed between high COX-2 expression in cecal polyps as compared with the polyps resected from the ascending (P <0.001), transverse (P <0.007), descending (P = 0.001), and sigmoid colon (P = 0.02), as well as from the rectum (P <0.02). Similarly, there was a statistically significant difference in high COX-2 expression between sigmoid and ascending colon-derived polyps (P <0.05). When resected adenomas were analyzed as a separate group, statistically significant differences in the occurrence of high COX-2 expression were observed between cecal adenomas as compared with adenomas

TABLE 2 Expression of cyclooxygenase-2 (COX-2) with regard to selected clinical and pathology parameters of the analyzed polyps

Parameter	n	Expression		*P*
		none/low, n (%)	high, n (%)	
sex				
F	95	46 (48)	49 (52)	NS
M	117	51 (44)	66 (56)	
size, mm				
<10	132	83 (63)	49 (37)	0.000001
≥10	80	14 (17)	66 (83)	
type of polyp				
hyperplastic	25	19 (76)	6 (24)	0.001
adenoma[a]	187	78 (42)	109 (58)	
degree of dysplasia				
low	141	74 (52)	67 (48)	0.000001
high	46	4 (9)	42 (91)	
localization within the colon[b]				
proximal part	67	33 (48)	34 (52)	NS
distal part	145	64 (45)	81 (55)	
number of polyps detected by colonoscopy				
1	80	34 (42)	46 (58)	NS
2–5	94	43 (46)	51 (54)	
6–10	23	13 (57)	10 (43)	
>10	15	7 (47)	8 (53)	
distribution of COX-2-positive cells within the polyp				
E	0	0	101 (88)	0.01
S	0	0	0 (0)	
E + S	0	0	14 (12)	
type of adenoma				
tubular	54	30 (56)	24 (44)	<0.001
tubulovillous	48	12 (25)	36 (75)	
villous	12	0 (0)	12 (100)	
serrated	69	36 (52)	33 (48)	

a including 4 cases of intramucosal carcinoma
b with relation to the splenic flexure

Abbreviations: E – epithelium, F – female, M – male, NS – nonsignificant, S – stroma

resected from the ascending (P <0.002), transverse (P <0.05), descending (P = 0.0002), and sigmoid colon (P <0.05), as well as when high COX-2 expression in adenomas resected from the rectum and descending colon (P <0.004), sigmoid and descending colon (P = 0.003), transverse and descending colon (P <0.02), rectum and ascending colon (P <0.04), and sigmoid and ascending colon (P <0.04) was compared. The other differences were not statistically significant. We did not observe any significant differences in COX-2 expression when comparing the left and right colon.

Distribution of highly COX-2-positive cells within the polyps In 101 of 115 polyps (88%) characterized by high COX-2 expression, COX-2-positive cells were detected only in the epithelium, while in 15 polyps (12%) such cells were distributed equally in the epithelium and stroma. The observed difference was statistically significant (P = 0.01). Interestingly, we did not observe polyps only with stromal expression of positive cells.

There was no statistically significant difference in high expression of COX-2 with regard to patients' sex, age, or the total number of polyps and adenomas detected during colonoscopy. The results are presented in TABLE 2.

DISCUSSION Several studies published so far have provided ample evidence for the role of COX-2 in the development of colorectal cancer. Moreover, high expression of COX-2 correlates with poor prognosis in this disease.[5,13,18-25] However, there is a paucity of data elucidating the relationship between high expression of this enzyme and the development of colorectal polyps and their transformation into CRC. Our study, which analyzed 212 polyps (including 187 adenomas), represents the largest effort in this field so far. High expression of COX-2 was detected in 54% of the tested polyps, which is in agreement with the existing reports indicating 54% to 91% of the polyps to be COX-2 positive. High COX-2 expression correlated with histological type, degree of epithelial dysplasia, as well as the size and location of the polyps within the colon.

We observed high expression of COX-2 in all polyp types; however, hyperplastic polyps were characterized by the lowest percentage of positive samples (24%). To our knowledge, our study has been the first to assess and detect the expression of this inflammation-modulating enzyme in hyperplastic polyps. Also known as metaplastic, these polyps were traditionally considered to be benign, but they have been recently associated with several irregularities typical for early carcinogenic processes, such as mutations in protooncogenes *K-ras* and *BRAF*, microsatellite instability, DNA methylation, and loss of heterozygosity on chromosome 1p.[26-31] Moreover, defective apoptosis has been observed in the epithelial cells of hyperplastic polyps.[26] High COX-2 expression detected in some of the hyperplastic polyps may suggest the involvement of inflammatory processes in early carcinogenesis.

High expression of COX-2 occurred more often in adenomas (in almost 60%), which is in line with the study by Wu et al.,[11] who reported 58% of all adenomas, regardless of their histological type, to be positive for COX-2. Further analysis revealed that all villous adenomas, long considered to carry the highest risk for malignant transformation, were positive for COX-2. The remaining histological types, i.e., tubulovillous, tubular, and serrated adenomas, were also positive for COX-2, although at a lower rate (75%, 44%, and 48%, respectively). Our results confirm the previous report by Fujita et al.,[10] who observed more frequent COX-2 expression in tubulovillous adenomas as compared with tubular adenomas. In contrast, Pisano et al.[14] and Einspahr et al.,[19] who analyzed 68 and 108 adenomas, respectively, did

TABLE 3 High expression of cyclooxygenase-2 (COX-2) in colon polyps as reported by other authors

Author	Number of polyps	% of polyps with high expression of COX-2
Pisano, 2005[14]	68	91
Hao, 1999[24]	85	89
Chapple, 2000[9]	58	77
Elder, 2002[32]	35	68
Fujita, 2000[10]	29	62
Wu, 2003[11]	19	58
Kim, 2004[33]	57	54
Wasilewicz (current study)	212	54

not find any correlation between upregulated COX-2 and these 2 types of adenomas. Unfortunately, other histological types were not included in their analyses. Interestingly, we did not observe statistically significant differences in enzyme expression between tubular adenomas and hyperplastic polyps. This novel finding may suggest much lower potential of nonvillous adenomas to undergo malignant transformation.

We established a correlation between COX-2 expression and epithelial dysplasia. While almost 50% of the polyps characterized by low-grade epithelial dysplasia were positive for COX-2, over 90% of specimens with high-grade dysplasia showed high levels of this enzyme as compared with only 24% of COX-2-positive specimens without dysplasia. Fujita et al.[10] did not observe such correlation, possibly because of a small sample size (29 polyps).

Similarly to other reports, we observed a relationship between COX-2 expression and the size of the polyp.[14,25,26,32] The majority of polyps and adenomas larger than 10 mm were strongly positive for COX-2.

We did not observe significant differences in COX-2 expression with regard to the location of polyps or adenomas within the left or right colon, which confirmed the results obtained by Pisano et al.[14] Einspahr et al.[19] and Kim et al.[33] observed a correlation between higher COX-2 expression and distal location of the polyp within the colon. Such discrepancies can possibly be explained by the differences in sample sizes and the ethnicity of the patient groups (Polish, Italian, Korean).

We did not observe any correlations between COX-2 expression and the sex and age of patients undergoing polypectomy, which is in line with the only study previously published on the subject.[14]

COX-2-positive cells were most frequently observed in the epithelium, and the distribution of positive cells both in the epithelial and stromal layer was significantly less common. We did not observe COX-2 expression that would be limited only to the stromal layer.

So far, only Elder et al.[32] reported similar findings to ours. Bamba et al.[34] and Chapple et al.[9] observed COX-2-positive cells within the epithelium, but both studies underlined the predominance of such cells within the stromal layer. Likewise, Hardwick et al.[35] and Tanaka et al.[36] detected high expression of the enzyme by the stromal macrophages. Arnoletti et al.[37] described dominant COX-2 expression within the stromal layer and suggested a possible correlation between epithelial location of COX-2-positive cells and malignant transformation of the adenoma. Our results indicate that epithelial location of high COX-2 expression is characteristic for adenomas with low-grade dysplasia and for hyperplastic polyps. This might indicate predominant epithelial expression of COX-2 as a possible marker of polyp formation rather than the malignant transformation of preexisting adenomas. The discrepancies between the available studies can certainly be attributed to the use of various laboratory methods assessing enzyme expression (immunohistochemistry, molecular assays, staining with either monoclonal or polyclonal antibodies), and to the involvement of other biological factors affecting the expression of enzymes. The issue requires further studies, although Dixon et al.[38] reported quantitative differences between the expression of COX-2 and the levels of COX-2 mRNA, which could at least in part explain the discrepancies between the available studies.

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ARTYKUŁ ORYGINALNY

Ekspresja cyklooksygenazy-2 w polipach jelita grubego

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SŁOWA KLUCZOWE

cyklooksygenaza-2, immunohistochemia, karcynogeneza, polipy jelita grubego

STRESZCZENIE

WPROWADZENIE Dane dotyczące związków cyklooksygenazy-2 (COX-2) z powstawaniem raka jelita grubego są ograniczone.

CELE Celem pracy było zbadanie ekspresji cyklooksygenazy-2 (COX-2) w polipach jelita grubego o różnej budowie histologicznej, określenie związku między ekspresją tego enzymu a wybranymi czynnikami patologicznymi i klinicznymi charakteryzującymi polipy oraz ustalenie, w której części polipa są zlokalizowane komórki z dużą ekspresją COX-2.

PACJENCI I METODY Zbadano 212 polipów jelita grubego pobranych od 175 pacjentów. Wykonano barwienia immunohistochemiczne przy użyciu przeciwciał monoklonalnych anty-COX-2.

WYNIKI Statystycznie istotne różnice związane z wysoką ekspresją COX-2 stwierdzono: w gruczolakach w porównaniu z innymi polipami ($P < 0{,}001$), w gruczolakach z dużą dysplazją ($P < 0{,}000\,001$) oraz w polipach zlokalizowanych w kątnicy ($P < 0{,}02$). Statystycznie istotnie różnice miały również związek z wielkością polipa ($P < 0{,}000\,001$). Komórki z wysoką ekspresją COX-2 najczęściej występowały w nabłonku polipa ($P = 0{,}01$). Nie stwierdzono istotnych zależności między wysoką ekspresją COX-2 a wiekiem oraz płcią pacjentów i całkowitą liczbą polipów.

WNIOSKI Wykazano związek między wysoką ekspresją COX-2 a typowymi czynnikami ryzyka transformacji złośliwej polipów jelita grubego. Wyniki sugerują udział COX-2 we wczesnych etapach karcynogenezy w jelicie grubym.

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