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## COMPARATIVE IMMUNOHISTOCHEMICAL STUDY OF KI-67, P53, CASPASE-3 IN DISTAL COLONIC POLYPS AND COLORECTAL ADENOCARCINOMA

Shyskin M.A.  Comparative immunohistochemical study of ki-67, p53, caspase-3 in distal colonic polyps and colorectal adenocarcinoma.

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**ABSTRACT. Background.** Colorectal carcinogenesis is a multistep process that begins from the normal epithelium and includes the step of adenoma formation. The question of diagnostic and prognostic value of proliferation and apoptosis markers for the distal colorectal neoplasms is still open. **Objective.** To compare Ki-67, p53, caspase-3 expression levels in distal colonic polyps and colorectal adenocarcinoma. **Methods.** Pathomorphological and immunohistochemical studies of biopsies of distal colonic polyps from 30 patients and surgical material of colorectal adenocarcinoma from 30 patients were carried out. **Results.** Ki-67 expression level by epitheliocytes of hyperplastic polyps is 1.5 times lower than that for adenocarcinoma [26.23 (22.16, 48.88) % vs. 41.20 (36.62, 59.42) %], but adenomas are distinguished by 1.5 times higher Ki-67 expression level in comparison with adenocarcinoma [62.40 (48.65, 76.23) % vs. 41.20 (36.62, 59.42) %]. Caspase-3 expression level by hyperplastic polyps epitheliocytes is 1.7 times lower than that for adenocarcinoma [16.99 (11.86, 39.85) CUOD vs. 28.72 (15.84, 76.71) CUOD], but caspase-3 expression level by epitheliocytes of adenomas is 1.1 times higher than that for cancer cells [31.84 (19.53, 42.34) CUOD vs. 28.72 (15, 84; 76.71) CUOD]. The maximum proliferation and apoptosis levels were revealed for high-grade [76.23 (62.36, 85.36) % and 42.34 (33.78, 65.38) CUOD] and villous [79.09 (69.12, 84.27) % and 67.88 (63.92, 71.29) CUOD] adenomas. p53 expression level by epithelial cells of hyperplastic polyps almost is 40 times lower than that for adenocarcinoma [0.00 (0.00; 1.47) % vs. 39.67 (15.69, 83.75) %], and p53 expression level by epitheliocytes of adenomas is 16.5 times lower than that for cancer cells [2.39 (1.58, 8.26) % vs. 39.67 (15.69, 83.75) %]. **Conclusion.** The high levels of proliferation and apoptosis of epitheliocytes characterize the polyps-precursors of colorectal carcinoma that have the biggest malignant potential. Colorectal adenocarcinoma differs by the medium p53 expression level by tumor cells.

**Key words:** colon, intestinal neoplasms, polyps, adenocarcinoma, cell proliferation, apoptosis.

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### Introduction

According to the American Cancer Society forecast 135,430 new cases of colorectal cancer (CRC) as well as 50,260 deaths from this disease will be registered in the USA during the 2018 year [1]. According to the National Cancer Registry of Ukraine CRC is on the list of 10 most common cancer sites among the population, constantly occupying a leading position among the causes of death for men and women [2].

B. Vogelstein et al. (1988) presented the model according to which colorectal carcinogenesis is a multistep process that begins from the normal epi-

thelium, develops over several years, and includes the step of adenoma formation [3]. This model still hasn't lost a relevance; however, it was supplemented by several studies relating to the molecular-genetic basis of colorectal carcinogenesis. Moreover, the idea about polyps that might be precursors for colorectal carcinoma changed as well. Nowadays both adenomatous (tubular, villous, and tubulovillous) and serrated (hyperplastic, traditional serrated, and sessile serrated adenomas) polyps are considered as potential precursors for colorectal cancer [4].

The classification of colonic polyps is based on

histomorphological features of them and differences between subsequent stages of carcinogenesis [5]. The adenomas main characteristic is dysplastic changes of epithelium that forms tubular or villous structures. Malignization of adenomas presents the classic sequence «adenoma – carcinoma» that realizes through mutations of *APC* gene followed by activation of the Wnt/ $\beta$ -catenin signaling pathway as well as mutations of *KRAS*, *PIK3CA* genes and other genes in more rare cases [6]. Serrated polyps are distinguished by the typical serrated appearance of the epithelial layer. The different histological types of these polyps are considered as consecutive stages of polyp progression; each of them is characterized by the bigger expression of dysplastic changes [5]. Malignization of serrated polyps is realized through mutations of *KRAS* and *BRAF* genes followed by activation of MAPK-signaling pathway [6].

There are universal mechanisms that occur during malignant transformation of adenomas and serrated polyps. These mechanisms include malfunctions of proto-oncogenes, oncosuppressor genes, proapoptotic and antiapoptotic genes, the normal function of which provides the balance between proliferation and apoptosis of epitheliocytes [7]. It's known that malignization of colonocytes is associated with abnormalities of *MKI67*, *TP53*, *CASP3*, *APAF1*, *ETS1*, *DCC*, *PTEN* genes function as well as the proteins coded by them [7, 8]. Herewith, there aren't so many studies that are devoted to the comparative characteristic of proliferative and apoptotic properties of adenomas, serrated polyps and CRC; the question of diagnostic and prognostic value of proliferation and apoptosis markers for the distal colorectal neoplasms is still open.

**Objective** – to compare Ki-67, p53, caspase-3 expression levels in distal colonic polyps and colorectal adenocarcinoma.

#### **Subject and methods**

Pathomorphological and immunohistochemical studies of biopsies of distal colonic polyps from 30 patients who undergo endoscopic procedure with polypectomy and surgical material of colorectal adenocarcinoma from 30 patients who undergo operation apropos the tumor of I-IV clinical stages were carried out.

Microstructure of the neoplasms was evaluated in paraffin sections that were dyed by hematoxylin and eosin and also by PAS-reaction. Immunohistochemical (IHC) study was carried out in dewaxed sections after their temperature demasking and suppressing of endogenous peroxidase activity. The studying of proliferative activity was carried out using monoclonal antibodies Mo a-Hu Ki-67 Antigen (Clone MIB-1, DAKO, Denmark), p53 accumulation – using monoclonal antibodies Mo a-Hu p53 Protein (Clone DO-7, DAKO, Denmark), apoptotic level – using monoclonal antibodies Mo a-Hu Caspase Ab-3 (Clone 3CSP03, Thermo Scientific, USA). Visualization system

DAKO EnVision+ System with diaminobenzidine (DAKO, Denmark) was also used. Results of the IHC study were evaluated using the Axioplan 2 microscope (Carl Zeiss, Germany); microslides were photographed by digital camera “Canon EOS 1000D” (Japan) with an increasing of x200, in five fields of view in each case.

The nuclear expression of Ki-67 and p53 markers was evaluated using Photoshop CC (2014) in digital images of the microslides. p53 expression level was estimated as low if it was less than 25% of immunopositive cells in a field of view, the expression level was estimated as medium if it was 25-75% of immunopositive cells in a field of view, and the expression level was estimated as high if it was more than 75% immunopositive cells in a field of view. Proliferative activity of the polyps and carcinoma cells was expressed as proliferation index (PI) that is the percent of cells with nuclear Ki-67 expression [9, 10]. Numerical indicators for gradation of Ki-67 expression level are the same as for p53.

Nuclear-cytoplasmic expression of caspase-3 was evaluated using the digital morphometry method. Caspase-3 expression level was expressed in the conventional units of the optical density (CUOD) and was graduated on the four levels: the lack of expression – 0-20 CUOD, the low caspase-3 expression level – 21-50 CUOD, the moderate – 51-100 CUOD, and the high caspase-3 expression level – more than 100 CUOD.

Statistical processing of the results was performed on a personal computer using program “Statistica® for Windows 13.0” (StatSoft Inc., License № JPZ804I382130ARCN10-J). The median (Me), the lower and the upper quartiles (Q1; Q3) were calculated. Comparison was performed using the Mann-Whitney U-test and the Kruskal–Wallis test by ranks. The results were considered as statistically significant when  $p < 0,05$ .

#### **Research results and discussion**

According to the results of pathohistological study it was revealed that 73,33% of distal colonic polyps (DCP) presented by adenomas and 26,67% of the polyps presented by hyperplastic polyps. IHC study made it possible to establish that DCP are characterized by the medium PI of epitheliocytes and the low PI of stromal cells, the low levels of p53 expression by epithelial and stromal cells as well as the low level of epithelial and stromal cells apoptosis. These data are shown in the *Table 1*.

The features of IHC expression of proliferation and apoptosis markers in DCP without dysplasia, with dysplasia, as well as in DCP with different grade of dysplastic changes and in DCP of different histological types were described in the previous study [11].

According to the results of IHC study it was revealed that colorectal adenocarcinoma (CRA) is characterized by the medium PI of cancer cells and the low PI of stromal cells, by the medium level of

p53 accumulation in cancer cells and the low level of p53 accumulation in stromal cells, and by the low levels of apoptosis of CRA cells. These data are

shown in the Table 2. The features of IHC expression of proliferation and apoptosis markers in CRA were described in the previous article [12].

Table 1  
The indicators of Ki-67, p53, caspase-3 immunohistochemical expression levels in cells of distal colonic polyps

DCP	Adenomas		Hyperplastic polyps	
	Epitheliocytes	Stromal cells	Epitheliocytes	Stromal cells
Ki-67 (%)	62,40 (48,65; 76,23)	2,94 (1,23; 4,35)	26,23 (22,19; 48,88)	1,18 (1,10; 1,86)
p53 (%)	2,39 (1,58; 8,26)	1,23 (0,72; 1,49)	0,00 (0,00; 1,47)	0,00 (0,00; 0,05)
caspase-3 (CUOD)	31,84 (19,53; 42,34)	43,87 (25,47; 73,09)	16,99 (11,86; 39,85)	28,64 (19,20; 30,71)

Table 2  
The indicators of Ki-67, p53, caspase-3 immunohistochemical expression levels in cells of colorectal adenocarcinoma

Cells	Cancer cells	Stromal cells
Ki-67 (%)	41,20 (36,62; 59,42)	5,23 (4,72; 6,45)
p53 (%)	39,67 (15,69; 83,75)	0,03 (0,00; 2,57)
caspase-3 (CUOD)	28,72 (15,64; 76,71)	37,78 (26,27; 54,60)

A line of statistically significant differences between the data obtained for CRA and distal colonic adenomas was revealed using the Mann-Whitney U-test. It was established that CRA distinguishes by the lower PI of epithelial cells [(41,20 (36,62; 59,42) % in CRA vs. 62,40 (48,65; 76,23) % in adenomas, ( $p < 0,05$ )], by the higher PI of stromal cells [5,23 (4,72; 6,45) % in CRA vs. 2,94 (1,23; 4,35) % in adenomas, ( $p < 0,05$ )], and by the higher level of p53 accumulation in epitheliocytes [39,67 (15,69; 83,75) % in CRA vs. 2,39 (1,58; 8,26) % in adenomas, ( $p < 0,05$ )].

According to results of comparative analysis for CRA and hyperplastic polyps it was revealed that the tumor distinguishes by the higher PI of stromal cells [5,23 (4,72; 6,45) % in CRA vs. 1,18 (1,10; 1,86) % in hyperplastic polyps, ( $p < 0,05$ )], by the higher apoptotic activity of stromal cells [37,78 (26,27; 54,60) CUOD in CRA vs. 28,64 (19,20; 30,71) CUOD in hyperplastic polyps, ( $p < 0,05$ )], and by the higher level of p53 accumulation in epithelial cells [39,67 (15,69; 83,75) % in CRA vs. 0,00 (0,00; 1,47) % in hyperplastic polyps, ( $p < 0,05$ )].

Moreover, a line of statistically significant differences between the data obtained for CRA and distal colonic adenomas with dysplastic changes of different grade was revealed using the Kruskal-Wallis test by ranks. It was revealed that maximum values of PI and apoptosis level are characteristic for high-grade adenomas epitheliocytes [76,23 (62,36; 85,36) % and 42,34 (33,78; 65,38) CUOD, respectively]; maximum level of p53 accumulation is characteristic for CRA epitheliocytes [39,67 (15,69; 83,75) %]. Low-grade adenomas are characterized by the minimum PI, p53 accumulation, and apopto-

sis levels [49,19 (43,08; 65,39) %, 1,86 (1,39; 5,25) %, and 42,34 (33,78; 65,38) CUOD, respectively]. These data are shown in the Fig. 1 – Fig. 9.

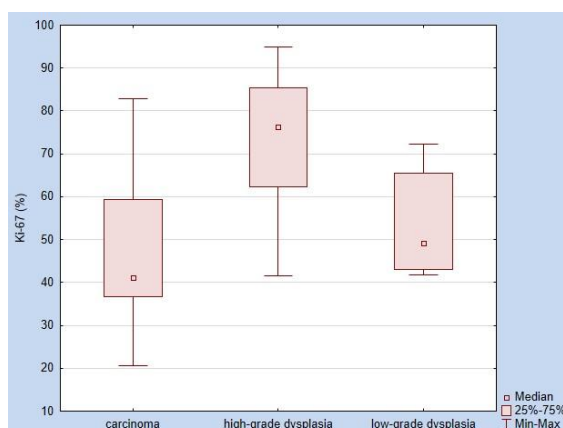


Fig. 1. The indicators of Ki-67 expression by cancer cells, epitheliocytes of high-grade adenomas and low-grade adenomas.

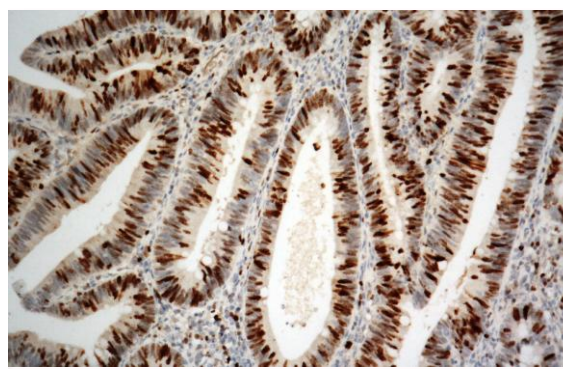


Fig. 2. Ki-67 expression in high-grade adenoma.

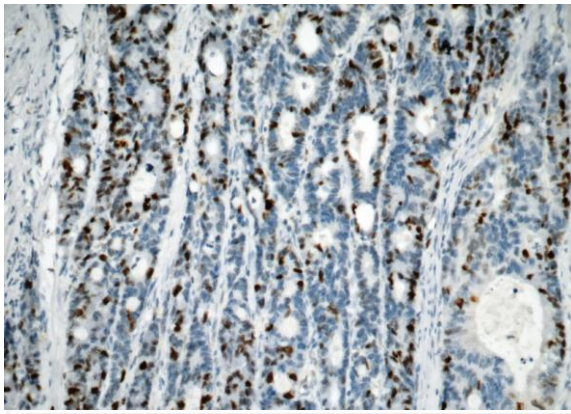


Fig. 3. Ki-67 expression in colorectal adenocarcinoma.

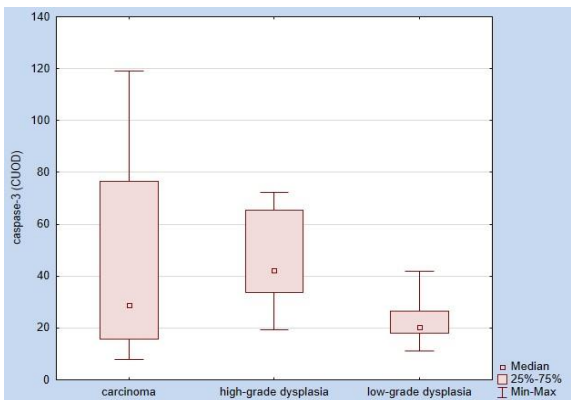


Fig. 4. The indicators of caspase-3 expression by cancer cells, epitheliocytes of high-grade adenomas and low-grade adenomas.

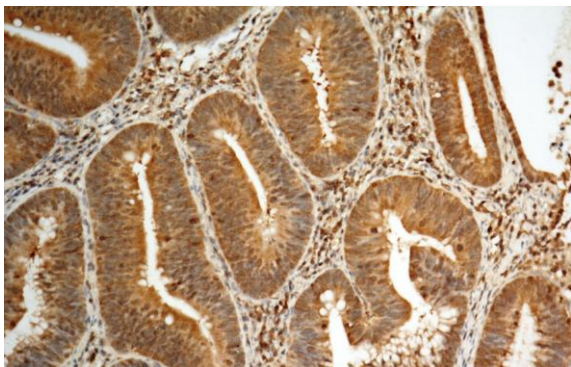


Fig. 5. Caspase-3 expression in high-grade adenoma.

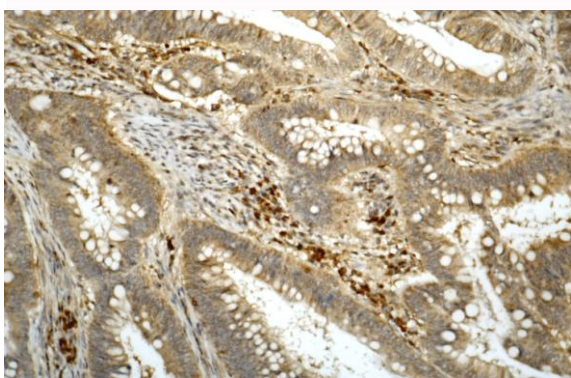


Fig. 6. Caspase-3 expression in colorectal adenocarcinoma.

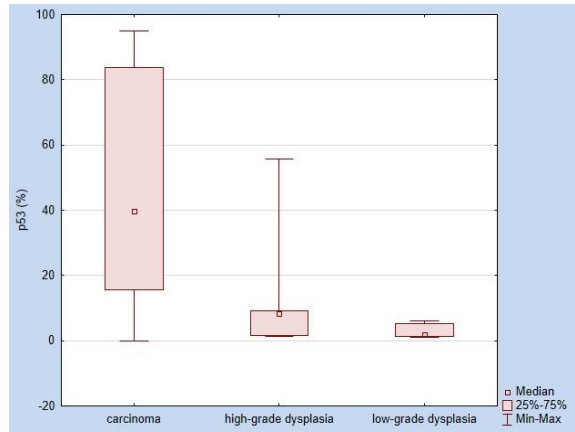


Fig. 7. The indicators of p53 expression by cancer cells, epitheliocytes of high-grade adenomas and low-grade adenomas.

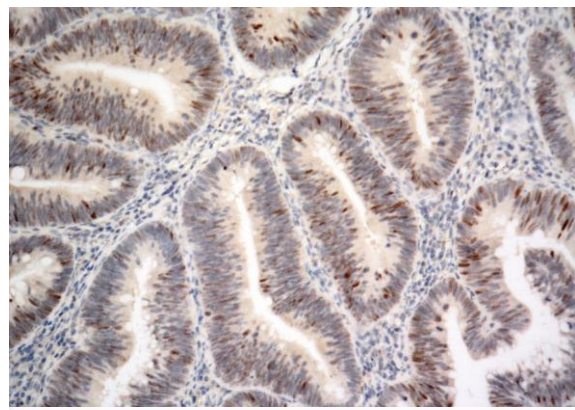


Fig. 8. p53 expression in high-grade adenoma.

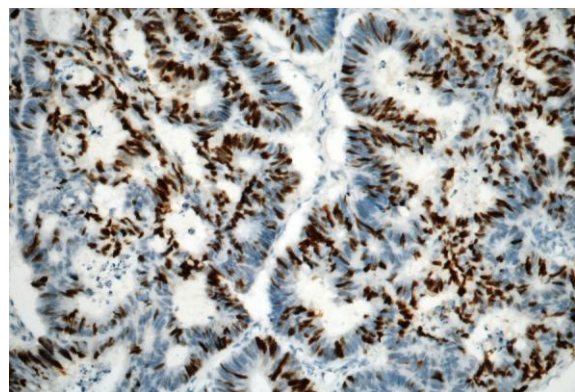


Fig. 9. p53 expression in colorectal adenocarcinoma.

Comparative analysis of the data obtained for CRA and different histological types of adenomas was also carried out. It was revealed that the maximum PI and apoptosis level are characteristic for epitheliocytes of villous adenomas [79,09 (69,12; 84,27) % and 67,88 (63,92; 71,29) CUOD, respectively]; maximum p53 accumulation level is characteristic for cancer cells [39,67 (15,69; 83,75) %]. The minimum PI was revealed in cancer cells [41,20 (36,62; 59,42) %]; the minimum p53 accumulation and caspase-3 expression level are characteristic for tubular adenomas [2,35 (1,53; 5,62) % and 20,38

(18,08; 26,52) CUOD, respectively]. These data are shown in the Fig. 10, Fig. 11, Fig. 12.

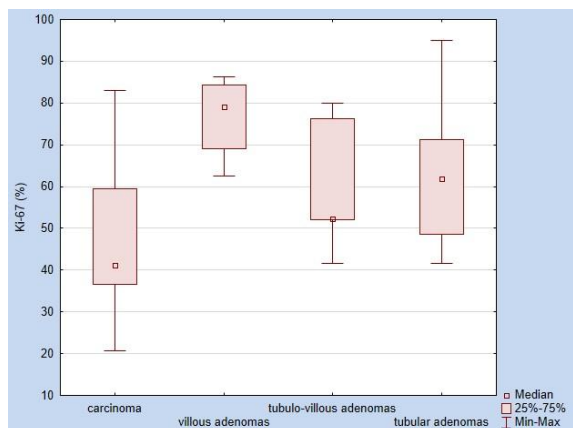


Fig. 10. The indicators of Ki-67 expression by cancer cells, epitheliocytes of villous adenomas, tubulovillous adenomas, and tubular adenomas.

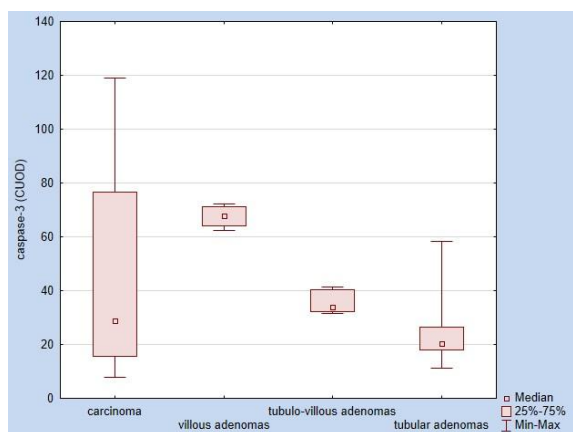


Fig. 11. The indicators of caspase-3 expression by cancer cells, epitheliocytes of villous adenomas, tubulovillous adenomas, and tubular adenomas.

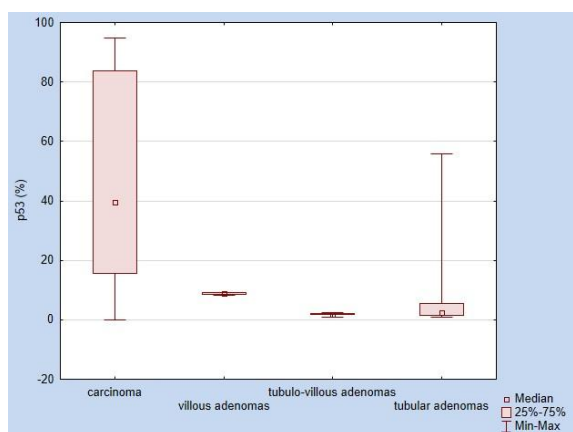


Fig. 12. The indicators of p53 expression by cancer cells, epitheliocytes of villous adenomas, tubulovillous adenomas, and tubular adenomas.

According to the literature data Ki-67 IHC expression increases progressively in the sequence «adenoma–carcinoma» [13, 14]. In this study it was revealed that Ki-67 expression level by epithelial cells of hyperplastic polyps is 1.5 times lower than

that for colorectal adenocarcinoma [26.23 (22.16, 48.88) % vs. 41.20 (36.62, 59.42) %,  $p < 0.05$ ], but adenomas are distinguished by 1.5 times higher Ki-67 expression level in comparison with colorectal adenocarcinoma [62.40 (48.65, 76.23) % vs. 41.20 (36.62, 59.42) %,  $p < 0.05$ ]. The maximum median of Ki-67 expression was established for villous adenomas – 79,09 (69,12; 84,27) %. Therefore, the maximum value of proliferative activity characterizes the polyps-precursors of CRA that have the biggest malignant potential. Consequently, it can be assumed that the highest level of proliferation is typical for the earliest stages of colorectal carcinogenesis. According to the literature data, activation of proliferation in progressive colonic adenomas is mediated by APC genes mutations in 70% of cases, that leads to permanent activation of Wnt/ $\beta$ -signaling pathway [15]. According to the obtained results, there is a mechanism, which inhibits proliferation activity after malignant transformation of high-grade adenoma. But similar results have not been described before, so, the mechanism is still unknown.

Talking about the statistically significant difference between the proliferation activity levels of hyperplastic polyps and adenomas [26,23 (22,16; 48,88) % vs. 62,40 (48,65; 76,23) %,  $p < 0,05$ ], it should be noted that Y. Fujimori et al. (2012) have already offered this index (PI) as a differential diagnostic criteria for the distal colonic polyps [16].

According to the literature data caspase-3 expression in colonic polyps is higher than in normal mucosa, but in CRA it's higher than in colonic polyps [17]. In this study it was revealed that caspase-3 expression level by epithelial cells hyperplastic polyps is 1.7 times lower than that for colorectal adenocarcinoma [16,99 (11,86, 39,85) CUOD vs. 28,72 (15,84, 76,71) CUOD,  $p < 0,05$ ], but caspase-3 expression level by epitheliocytes of adenomas is 1.1 times higher than that for cancer cells [31,84 (19,53, 42,34) CUOD vs. 28,72 (15, 84; 76,71) CUOD,  $p < 0,05$ ]. The maximum apoptosis level, by analogy with the proliferative activity level, was established for high-grade adenomas [42,34 (33,78; 65,38) CUOD]. Thus, these data do not correspond to the literature data, but have grounding on the results of our previous study [11]: it has been shown that there is a direct medium correlation between proliferation and apoptosis levels in distal colonic adenomas ( $r = 0,61$ ). Consequently, increasing proliferation is associated with increasing apoptosis of adenoma's epithelial cells.

According to the literature data p53 expression increases in the sequence «adenoma–carcinoma» [7, 6, 13, 14]. In this study it was revealed that p53 expression by CRA epitheliocytes is 16,5 times higher than that for adenomas [39,67 (15,69; 83,75) % vs. 2,39 (1,58; 8,26) %,  $p < 0,05$ ] and also is 40 times higher than that for hyperplastic polyps [39,67 (15,69; 83,75) % vs. 0,00 (0,00; 1,47) %,  $p < 0,05$ ]. The similar tendency was shown in the research of

our colleagues: p53 expression increases in the sequence «hyperplastic polyp – dysplastic polyp – non-invasive adenocarcinoma – invasive adenocarcinoma» of the stomach [18, 19]. Thereby, the results are consistent with current literature and indicate that CRA epitheliocytes distinguish by the prominent tendency to p53 accumulation, whereas epitheliocytes of benign polyps characterize by the low level of p53 expression.

#### Conclusions

1. Distal colonic polyps and colorectal adenocarcinoma are characterized by the medium level of epitheliocytes' proliferative activity, wherein Ki-67 expression level by the tumor cells is 1,5 times higher than that for hyperplastic polyps and 1,5 times lower than that for adenomas.

2. The low apoptosis level of epitheliocytes is characteristic for distal colonic polyps and colorectal adenocarcinoma, herewith caspase-3 expression level by the tumor cells is 1,7 times higher than that for

hyperplastic polyps and 1,1 times lower than that for adenomas.

3. High-grade adenomas and villous adenomas are distinguished by the high levels of epitheliocytes' proliferation and apoptosis.

4. Distal colonic polyps are characterized by the low level of p53 accumulation by epitheliocytes, whereas colorectal adenocarcinoma is characterized by the medium level of p53 accumulation by the tumor cells.

#### Information about conflicts of interest

Potential or explicit conflicts of interest related to this manuscript do not exist and are not foreseen at the time of publication.

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### **Шишкін М.А. Порівняльна імуногістохімічна характеристика Ki-67, p53, каспази-3 в поліпах та аденокарциномі дистальних відділів товстої кишки.**

**РЕФЕРАТ. Актуальність.** Колоректальний канцерогенез – це багатоступінчастий процес, який починається з нормального епітелію і включає стадію утворення аденоми. Питання про діагностичну та прогностичну цінність маркерів проліферації та апоптозу для колоректальних новоутворень лишається відкритим. **Мета.** Порівняти рівні експресії маркерів Ki-67, p53, каспази-3 в поліпах дистальних відділів товстої кишки і колоректальній аденокарциномі. **Методи.** Проведено патоморфологічне та імуногістохімічне дослідження біопсій поліпів дистальних відділів товстої кишки 30 пацієнтів, а також операційного матеріалу колоректальної аденокарциноми 30 пацієнтів. **Результати.** Рівень експресії Ki-67 епітеліоцитами гіперпластичних поліпів є в 1,5 нижчим за рівень експресії маркеру раковими клітинами аденокарциноми [26,23 (22,16; 48,88) % vs. 41,20 (36,62; 59,42) %], в той час як аденоми відрізняє в 1,5 вищий рівень експресії Ki-67 при порівнянні з карциномою [62,40 (48,65; 76,23) % vs. 41,20 (36,62; 59,42) %]. Максимальні показники рівнів проліферації та апоптозу виявлено в аденомах з тяжкою дисплазією [76,23 (62,36; 85,36) % та 42,34 (33,78; 65,38) УООЩ] і ворсинчастих аденомах [79,09 (69,12; 84,27) % та 67,88 (63,92; 71,29) УООЩ]. Рівень експресії p53 для гіперпластичних поліпів є майже в 40 разів нижчим за аналогічний показник для карциноми [0,00 (0,00; 1,47) % vs. 39,67 (15,69; 83,75) %], а рівень експресії p53 для аденом є в 16,5 разів нижчим за аналогічний показник для ракових клітин [2,39 (1,58; 8,26) % vs. 39,67 (15,69; 83,75) %]. **Висновок.** Високі рівні проліферації та апоптозу епітеліоцитів відрізняють поліпи-прекурсори колоректальної карциноми, що мають найбільший злоякісний потенціал. Колоректальна аденокарцинома відрізняється помірним рівнем експресії мутантного протеїну p53 пухлинними клітинами.

**Ключові слова:** товстий кишечник, новоутворення кишечника, поліпи, аденокарцинома, проліферація, апоптоз.

### **Шишкін М.А. Сравнительная иммуногистохимическая характеристика Ki-67, p53, каспазы-3 в полипах и аденокарциноме дистальных отделов толстого кишечника.**

**РЕФЕРАТ. Актуальность.** Колоректальный канцерогенез – это многоступенчатый процесс, который начинается с нормального эпителия и включает стадию образования аденомы. Вопрос о диагностической и прогностической ценности маркеров пролиферации и апоптоза для колоректальных новообразований остается открытым. **Цель.** Сравнить уровни экспрессии маркеров Ki-67, p53, каспазы-3 в полипах дистальных отделов толстого кишечника и колоректальной аденокарциноме. **Методы.** Проведено патоморфологическое и иммуногистохимическое исследование биопсий полипов дистальных отделов толстого кишечника 30 пациентов, а также операционного материала колоректальной аденокарциномы 30 пациентов. **Результаты.** Уровень экспрессии Ki-67 эпителиоцитами гиперпластических полипов в 1,5 раз ниже уровня экспрессии маркера раковыми клетками [26,23 (22,16; 48,88) % vs. 41,20 (36,62; 59,42) %], в то время как аденомы отличает в 1,5 раза более высокий уровень экспрессии Ki-67 при сравнении с карциномой [62,40 (48,65; 76,23) % vs. 41,20 (36,62; 59,42) %]. Максимальные показатели уровней пролиферации и апоптоза выявлено в аденомах с тяжелой дисплазией [76,23 (62,36; 85,36) % и 42,34 (33,78; 65,38) УООЩ], и ворсинчатых аденомах [79,09 (69,12; 84,27) % и 67,88 (63,92; 71,29) УООЩ]. Уровень экспрессии p53 для гиперпластических полипов практически в 40 раз ниже аналогичного показателя для карциномы [0,00 (0,00; 1,47) % vs. 39,67 (15,69; 83,75) %], а уровень экспрессии p53 для аденом в 16,5 раз ниже аналогичного показателя для раковых клеток [2,39 (1,58; 8,26) % vs. 39,67 (15,69; 83,75) %]. **Выводы.** Высокие уровни пролиферации и апоптоза эпителиоцитов отличают полипы-прекурсоры колоректальной аденокарциномы, имеющие наибольший злокачественный потенциал. Колоректальная аденокарцинома отличается средним уровнем экспрессии мутантного протеина p53 опухолевыми клетками.

**Ключевые слова:** толстый кишечник, новообразования кишечника, полипы, аденокарцинома, пролиферація, апоптоз.