Comparative Analysis of the Immunohistochemical Expression of the Parkin and APC proteins in Polyps and Colorectal Adenocarcinomas

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Abstract

Introduction Colorectal carcinoma is the result of a series of mutations based on the adenoma-carcinoma sequence. We aimed to perform a comparative analysis of the immune expression of the parkin (*PARK2* gene) and of the APC (*APC* gene) proteins in samples of colorectal polyps and adenocarcinomas.

Materials and Methods Through a tissue microarray, we reviewed by immunohistochemistry 284 polyps from 222 patients, as well as 73 colorectal samples of adenocarcinoma. Since more than one lesion was observed in more than half of the patients with polyps, we developed a multilevel linear regression statistical model to avoid interpretation bias.

Results In the univariate analysis comparing protein expression that adenocarcinomas presented a higher expression of parkin (6.19; 95% confidence interval [95%CI]: 4.43–9.95; $p = < 0.001$) and APC (13.5; 95%CI: 11–15.9; $p < 0.001$) than the polyps. Among the colorectal polyps, a positive correlation between parkin and APC expression (0.23; $p < 0.001$) was also found. There are no previous studies showing overexpression of such proteins in adenocarcinomas compared with neoplastic polyps.

Conclusion Parkin and APC showed a similar biological behavior in tumor suppression, with a tendency towards a de novo increase in their expression as the neoplastic cell advances in the oncogenic sequence. This indicates that parkin and APC may be involved in the late mechanisms of tumor progression control in the carcinogenesis pathway.

Keywords

- immunohistochemistry
- adenocarcinoma
- intestinal polyps
- colon
- rectum
- adenomatous polyposis coli

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Introduction

A marked decline in the colorectal cancer (CRC) burden was observed in the twentieth century,[1] probably due to the enhancement in colonoscopy screening programs and the improvement in treatment strategies.[2] Despite this, CRC remained the third leading cancer and second leading cause of cancer-related deaths worldwide in 2020.[3]

Many hereditary cancer syndromes have been implicated in the pathogenesis of CRC; however, most cases are sporadic.[4] It is believed that most CRC cases arise from precursor lesions, such as adenomas, and follow a predictive disease-progression model called the adenoma-carcinoma sequence. This model of carcinogenesis describes progressive phenotypic changes that reflect the acquisition of nonrandom somatic mutations.[5] Specifically, mutations in the *APC* gene are found in most CRC cases,[6] and the loss of its tumor-suppressive activity is considered a fundamental and early step in CRC carcinogenesis.[7] Since the first description of the adenoma-carcinoma sequence in 1988,[8] more than 20 genes involved in this pathway have been identified.[9]

Ubiquitin ligases (E3) are proteins involved in cellular responses to environmental stress and DNA damage, including the regulation of apoptotic pathways.[10] Impairment of E3 favors key processes of cellular carcinogenesis, including genetic instability and deregulated cellular proliferation.[10] One of the human E3 is parkin, a protein encoded by the *PARK2* (Parkinson disease [autosomal recessive, juvenile] 2) or *PRKN* (parkin RBR E3 ubiquitin protein ligase) gene. Parkin is present in an autoinhibited form,[11] and it has been postulated[12] that its activation occurs via posttranslational reversible changes in response to cell stress. A growing body of evidence suggests that *PARK2* is involved in diverse carcinogenic pathways, such as mitochondrial quality control, apoptosis, metabolism, and cell-cycle progression,[13] and that impaired *PARK2* expression promotes cancer progression.[14] *PARK2* is located in a chromosomal region prone to instability and breakages, called FRA6E, which has already been associated with cancer development.[15] A preclinical study[16] showed that parkin deficiency increases the susceptibility to cancer development in mice after exposure to an oncogenic insult. Deficiency in parkin expression has been found in various human cancers, including gliomas,[17,18] leukemia,[19] ovarian cancer,[15] lung cancer,[20,21] and hepatocarcinoma,[22,23] and previous evidence[13] has led to the belief that *PARK2* acts as a tumor suppressor gene.

Recent studies[24–27] have proposed a role for parkin in CRC development. Decreased parkin expression has been reported in colorectal precursor lesions in mice[24] and humans,[25] as well as in human CRC.[24,26,27] Parkin expression has been found to correlate with APC expression[24,26] and with a better prognosis in CRC.[26] However, the exact role of parkin in the adenoma-carcinoma sequence remains unknown. No previous studies have compared parkin expression in CRC to that in its precursor lesions to determine whether parkin expression changes during CRC carcinogenesis.

Purpose

The present study aimed to compare the immunohistochemical expression of parkin and APC in colorectal polyps and adenocarcinomas.

Materials and Methods

Study Design and Location

We performed an observational cross-sectional study using data collected from Hospital Santa Cruz and Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR), both located in the city of Curitiba, state of Paraná, Brazil. The study was approved by the Ethics in Research Committee of HC-UFPR (registered under no. 820.432, dated August 25, 2014), and informed consent was waived for all individuals included in the analysis.

Study Population and Data Collection

We obtained clinicopathological data from patients older than 18 years of age who underwent endoscopic polypectomy for neoplastic polyps at Hospital Santa Cruz in 2008 used in previous studies,[25,28,29] as well as from colorectal cancer surgery at HC-UFPR from 2007 to 2011. All available samples were included if the same patient had undergone polypectomy for more than one polyp. The exclusion criteria were: familial history adenomatous polyposis; previous treatment with radiotherapy or chemotherapy; polyps later diagnosed as inflammatory, hamartomatous, and pseudopolyps; and unavailability of pathological material for analysis.

The clinical data were obtained from medical records stored in the hospital database. All pathological samples were obtained from the Pathology Department of HC-UFPR.

Variables

We collected clinical data on age, sex, number of polyps, and diagnosis of adenocarcinoma. Age was stratified into 3 groups according to the Bethesda classification:[30] $\leq$ 45 years, 46 to 55 years, and $\geq$ 56 years. This classification considers that hereditary CRC commonly affects individuals younger than 45 years of age, whereas patients older than 56 years have a higher chance of developing sporadic CRC.

The pathological data included polyp/adenocarcinoma laterality, morphology, size, histology, grade, and immunohistochemical markers. Histological slides were analyzed by a pathologist with experience in gastrointestinal pathology for a diagnostic review.

We analyzed laterality as a dichotomous variable. Therefore, the right-colon neoplasms included appendiceal, cecal, ascending, hepatic flexure and proximal transverse colon neoplasms; and left-colon neoplasms included the distal transverse colon, splenic flexure, descending, sigmoid, rectosigmoid junction, and rectum (upper, middle and lower) neoplasms. We opted for this distribution following the current knowledge that right-sided colon lesions present distinct biological, epidemiological, and pathological characteristics, and usually a worse prognosis compared to left-sided colon cancers.[31,32]

The polyps were classified according to morphology into low-dysplasia adenomas (LDAs), high-dysplasia adenomas (HDAs), sessile-serrated polyps (SSPs), and hyperplastic polyps (HPs). The polyps and adenocarcinomas were stratified into low- and high-grade lesions. The expression of the parkin and APC proteins was determined using immunohistochemistry (IHC) slides.

Tissue Microarray and IHC

Tissue microarray (TMA) construction was performed at the Laboratory of Experimental Pathology of Pontifícia Universidade Católica do Paraná (PUCPR). We used archived formalin-fixed paraffin-embedded tissues to obtain cores measuring 3 mm in diameter. Histological slides were used to select areas with a better representation of the neoplastic tissue. The cores were then transferred to a recipient TMA paraffin block. Microsections were cut from the block to prepare hematoxylin-eosin and IHC slides. For the IHC, the slides were subjected to antigen retrieval with the Target Retrieval Solution (Dako, Glostrup, Denmark) and then incubated with the following monoclonal antibodies: antiparkin antibody (mouse; 1:100; Abcam Limited, Cambridge, United Kingdom) and anti-APC antibody (mouse; 1:200; Abcam Limited). A disclosure polymer (Spring Bioscience Corp., Pleasanton, CA, United States) was used as a secondary antibody. Slides were incubated with the diaminobenzidine complex and substrate and then counterstained with Harris hematoxylin. Positive and negative controls were included in the IHC analysis for each antibody. The slides were analyzed by an experienced pathologist.[28]

Morphometric Analysis of Parkin and APC

Parkin and APC protein expression was evaluated according to IHC using color morphometry, a quantitative technique that describes the area of protein expression in square micrometers (μm^2). For each slide, 3 pictures from each of the 4 image-wide fields were obtained. A BX40 microscope (Olympus Corporation, Hachioji, Tokyo, Japan) equipped with a 40× magnification objective lens and a Dino Eye camera (AnMo Electronics Corporation, Hsinchu City, Taiwan) using DinoCapture 2.0 software (AnMo Electronics Corporation) was used for image capture. The images were optimized using the Photoshop CS6 (Adobe Systems Incorporated, San Jose, CA, United States) software, version 13.0, by removing the stroma, mucin lakes, and white areas. The remaining regions of interest were then analyzed using the Image-Pro Plus (Media Cybernetics, Inc., Rockville, MA, United States) software with a color morphometric tool using a high-power field (HPF). ►**Figs. 1**, **2** show examples of morphometric analysis of colorectal polyps and adenocarcinomas.

Statistical Analysis

Considering that several patients contributed to the study sample with more than one polyp, it was necessary to analyze them within a statistical model that considered the hierarchical data structure to avoid possible analysis biases. To assess the association between clinicopathological parameters and IHC expression, we used a univariate multilevel linear regression model in which polyps were defined as level 1, and patients, as level 2. The significance of the variables was assessed using the Wald test, and the results were presented in terms of coefficient variables within 95% confidence intervals (95%CIs). The intraclass correlation coefficient was estimated to assess the composition of the variations in the markers. Pearson's correlation coefficients were used to assess the associations among quantitative variables. The Student's *t*-test and analysis of variance (ANOVA) were used to compare IHC markers between the groups. The Student's *t*-test, the Fisher's exact test, and the

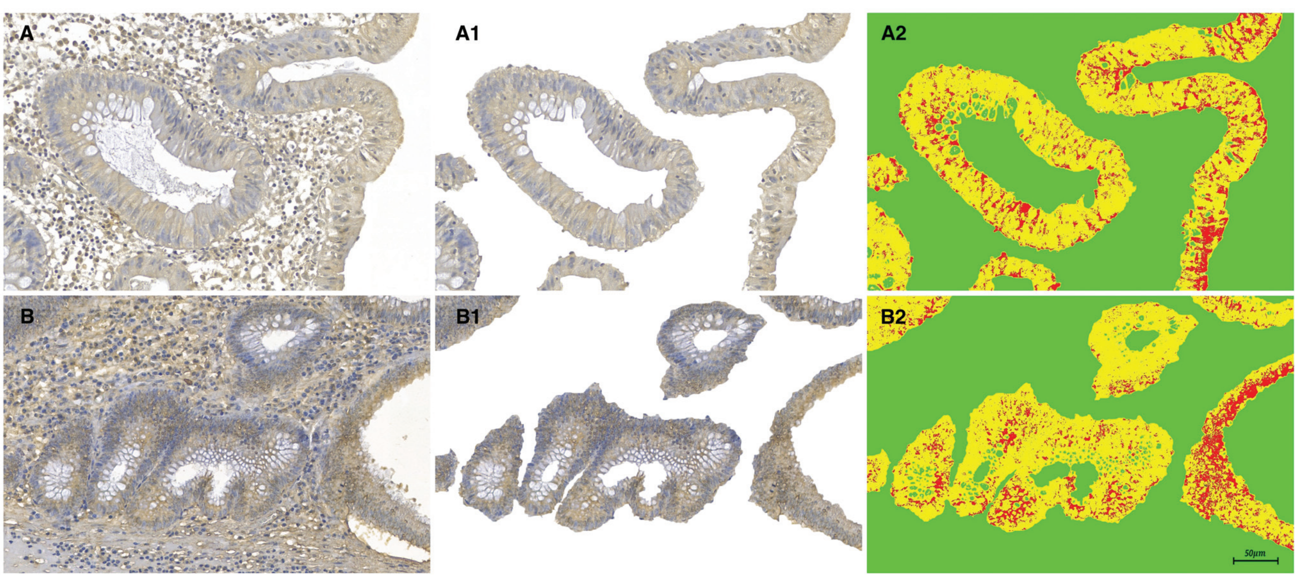

Fig. 1 Morphometric analysis of colorectal polyps (x40 magnification). (**A**) Parkin immunoexpression; (**B**) APC immunoexpression; (**A1,B1**) Image optimized with the Photoshop CS6 (Adobe Systems Incorporated) software, version 13.0, after removal of non-interest areas (stroma and mucin lakes), represented in white; (**A2,B2**) morphometric processing with the representation of non-interest areas in green, areas without protein expression, in yellow, and immunopositivity for immunohistochemical staining, in red.

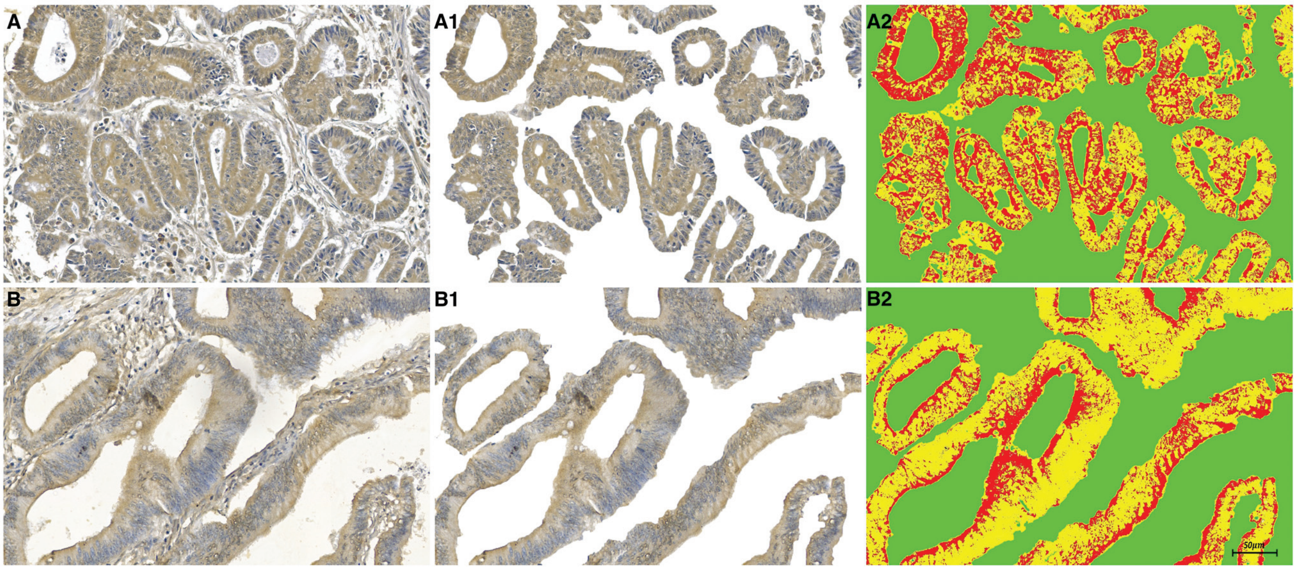

Fig. 2 Morphometric analysis of colorectal adenocarcinomas (x40 magnification). (**A**) Parkin immunoexpression; (**B**) APC immunoexpression; (**A1,B1**) Image optimized with the Photoshop CS6 (Adobe Systems Incorporated) software, version 13.0, after removal of non-interest areas (stroma and mucin lakes), represented in white; (**A2,B2**) morphometric processing with the representation of non-interest areas in green, areas without protein expression, in yellow, and immunopositivity for immunohistochemical staining, in red.

Chi-squared test were used for the comparison of groups defined by polyps and adenocarcinomas. Statistical significance was set at $p < 0.05$. Data were analyzed using the Stata (StataCorp LLC, College Station, TX, United States) software, version 14.

Results

We included 295 individuals, 222 (75.2%) of whom underwent polypectomy for neoplastic polyps, and 73 (24.7%) underwent colorectal cancer surgery for adenocarcinoma. The clinical characteristics of the sample are summarized in ►**Table 1**. Among the 222 (75.2%) individuals who underwent polypectomy, 122 (55%) presented more than 1 polyp. In total, 284 polyps were included in the study. A descriptive analysis of the neoplastic lesions is shown in ►**Table 2**.

Parkin and APC expression in high- and low-grade polyps and adenocarcinomas is shown in ►**Table 3**. We found a statistically significant difference in parkin expression between the lesions: in low-grade lesions, Parkin expression was higher in adenocarcinomas than in polyps ($p < 0.001$), and, in high-grade lesions, parkin expression was also higher among adenocarcinomas, although the difference was not statistically significant. No significant difference was found between polyps and adenocarcinomas when comparing low- and high-grade lesions. There was also a statistically significant difference in APC expression between the groups; it was

Table 1 Clinicopathological characteristics of the study population

	Polyp group ($N = 222$)		Adenocarcinoma group ($N = 73$)	
	n	%	n	%
Gender				
Male	122	55	34	46.6
Female	100	45	39	53.4
Age groups (years)				
≤ 45	45	20.3	13	17.8
46–55	58	26.1	12	16.4
≥ 56	119	53.6	48	65.8
Number of polyps				
1	100	45		
> 1	122	55		

Table 2 Descriptive analysis of neoplastic lesions

	Polyps ($N = 284$)		Adenocarcinomas ($N = 73$)	
	n	%	n	%
Location				
Right colon	121	42.6	18	24.7
Left colon	163	57.4	55	75.3
Grade				
Low	262	92.3	64	87.7
High	22	7.7	8	10.9
Unknown	0	0	1	0.1
Size (mm)				
< 4	68	23.9		
4–10	186	65.5		
> 10	30	10.6		
Morphology				
Pediculate	27	9.5		
Sessile	257	90.5		
Histology				
LGA	192	67.6		
SSP	25	8.8		
HGD	22	7.7		
HP	45	15.8		

Abbreviations: HGD, high-grade dysplasia; HP, hyperplastic polyp; LGA, low-grade adenoma; SSP, sessile serrated polyp.

higher in adenocarcinomas than in polyps in low- ($p < 0.001$) and high-grade ($p = 0.001$) lesions.

The results of the univariate multilevel linear regression for the comparison of protein expression showed that adenocarcinomas had a significantly higher expression of parkin (6.19; 95%CI: 4.43–9.95; $p < 0.001$) (►**Fig. 3A**) and APC (13.5; 95%CI: 11–15.9; $p < 0.001$) (►**Fig. 3B**) than polyps. Among the colorectal polyps, a positive correlation was found between parkin and APC expression (0.23; $p < 0.001$).

Discussion

We demonstrated a significant correlation between parkin and APC expressions in polyps and adenocarcinomas. Previous research[24] found that the deletion or alteration in the *PARK2* gene is intrinsically related to a deficiency in the expression of the *APC* gene, both of which cooperate to accelerate tumor progression. Accelerated adenoma progression and multiplicity in *APC* were found in mutant mice when *PARK2* knockout was present compared with those with an isolated *APC* mutation.[24] However, isolated parkin loss did not lead to adenoma development.[24] This suggests that *PARK2* loss plays an additive role in CRC development but is insufficient if not accompanied by other key genetic events. Genomic analyses[24] revealed a deficiency in *PARK2* expression in approximately one-third of sporadic CRC cases, and *PARK2* deficiency was found to be associated with *APC* deficiency.

This positive correlation was also found in another study[26] that observed higher expressions of the APC and parkin proteins in tumor and normal tissues respectively. Both studies[24,26] suggested that initial APC suppression can influence subsequent changes in parkin expression, which may be another mechanism by which parkin could be involved in cancer pathophysiology. Therefore, the tissue expression of parkin in colorectal polyps and adenocarcinomas is consistent with the expression of APC, a protein that is better established as a tumor suppressor. Regarding its role in the Vogelstein[8] tumor progression model, the *APC* mutation is admitted as an initial event in tumors of the "classic" pathway, that is, in the left colon. Thereafter, a sequence of events occurs at different stages of the evolution of a polyp until it accumulates enough mutations to present dysplasia, which will invariably progress to

Table 3 Protein expression of parkin and APC according to histology parameters and comparison of histology groups

	Mean	Median	SD	*p*	cLGP	cHGP	cLGA	cHGA
Parkin								
LGP ($n = 262$)	10.4	9.6	6.1	< 0.001*	–	0.217	< 0.001*	0.039*
HGP ($n = 22$)	12.2	11.3	6.1		0.217	–	0.005*	0.258
LGA ($n = 64$)	16.8	15.1	8.6		< 0.001*	0.005*	–	0.549
HGA ($n = 8$)	15.3	19.8	8.4		0.039*	0.258	0.549	–
APC								
LGP ($n = 240$)	18.8	18.3	7.3	< 0.001*	–	0.608	< 0.001*	< 0.001*
HGP ($n = 17$)	20	19.6	7.8		0.608	–	< 0.001*	0.001*
LGA ($n = 64$)	32.4	31.6	14		< 0.001*	< 0.001*	–	0.817
HGA ($n = 8$)	33.2	34.6	16.5		< 0.001*	0.001*	0.817	–

Abbreviations: c, *p*-value when compared with; HGA, high-grade adenocarcinoma; HGP, High-grade polyp; LGA, low-grade adenocarcinoma; LGP, low-grade polyp; SD, standard deviation. **Note:** * $p < 0.05$ (analysis of variance, ANOVA).

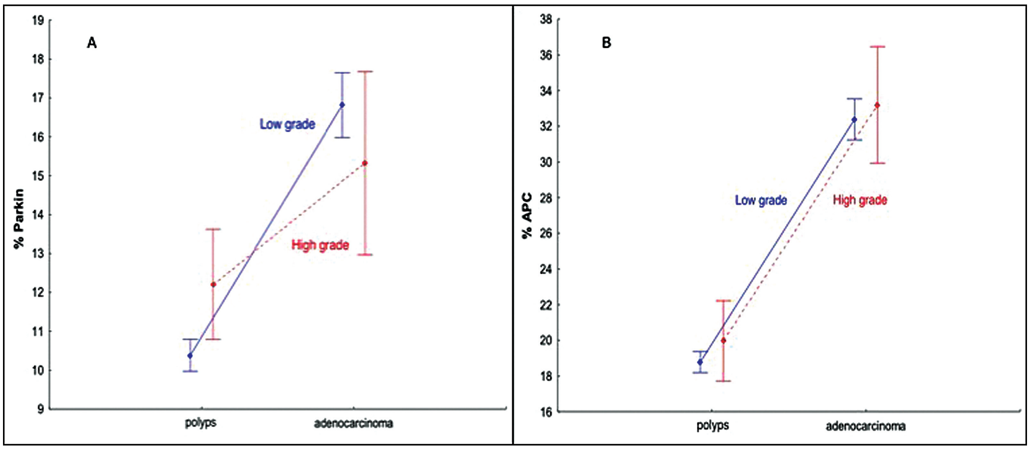

Fig. 3 Multilevel analysis of the combined effect of polyp/adenocarcinoma and the degree of differentiation of (**A**) parkin protein and (**B**) APC protein, showing in both graphics a significant ($p < 0.001$) lower expression in low- and high-grade polyps compared with adenocarcinomas. We can also observe a higher expression of parkin in high-grade polyps and in low-grade adenocarcinomas, as well as a higher expression of APC in high-grade polyps and adenocarcinomas.

carcinoma. We suggest that, in the initial stages of the Volgestein model, parkin has a tumor suppressor function, acting in conjunction with APC.

In addition, we observed a higher immunoexpression of parkin and APC in (high- and low-grade) adenocarcinomas than in polyps (with high- and low-grade dysplasia). There are no previous studies showing overexpression of such proteins in adenocarcinomas compared with neoplastic polyps. This suggests that, as a neoplastic polyp dedifferentiates toward the formation of adenocarcinoma, the expressions of parkin and APC increase, in contrast to what we initially expected. As both are products of tumor suppressor genes, when mutated, we expected that they would favor neoplastic evolution, thus being expressed in progressively smaller amounts. However, this assumption was not confirmed by the results observed. In fact, after the multilevel analysis with four subgroups of polyps and carcinomas, we confirmed that there was a greater expression of parkin and APC in the group of adenocarcinomas than in the polyp groups. Likewise, when analyzing the multilevel hierarchical structure for APC immunoexpression, a higher expression of this protein was identified in polyps, which is expected in the classic pathway of the carcinogenesis model. Thus, corroborating previous findings,[29] the results observed with these markers may be associated with the progression of precursor lesions to colorectal cancer. A recent study[25] reported high parkin expression in colonic polyps. On the other hand, other studies[26,27] found lower *PARK2* expression in adenocarcinomas than in normal tissue, and lower parkin protein expression levels in adenocarcinomas than in adjacent normal tissue.[26] However, as in the current study we did not compare the results with normal tissue and polyps may eventually show alterations, the results may suggest that the eventual mutation of these genes, which leads to an expected reduction in their expression in the first events of the classic pathway, paradoxically results in a subsequent increase in expression when the cell becomes malignant and has a high potential for tumor invasion and aggressiveness (poorly differentiated neoplasms). Thus, analyzing the expression of parkin transversally, it could be increased in normal tissue, decreased in polyps, and again increased in adenocarcinomas, trying to contain tumor progression, but with expression still below the levels found in normal tissue.

Another alternative is that parkin mediates mitochondrial mitophagy. Mitochondrial damage caused by changes in tumor cells can lead to increased generation of reactive oxygen species and alterations in membrane potential. Parkin ensures mitochondrial homeostasis by inducing mitophagy in damaged mitochondria through an increase in the BAX/BCL-2 ratio. Thus, it protects cells from apoptosis and contributes to cell viability and consequent tumor progression.[33] In an antagonistic manner, high levels of parkin in adenocarcinomas could contribute to tumor progression, resulting in increased expression accompanied by tumor progression.

However, it is important to note that the immunohistochemical analysis performed did not enable us to investigate whether the expressed protein was functional. Additional studies are needed to identify the functionality of this protein.

Therefore, we conclude that parkin and APC have a similar biological behavior in tumor suppression, but with a tendency towards a "de novo" increase in their expression as the neoplastic cell advances in the adenoma-carcinoma sequence. These findings indicate that parkin and APC may be involved in the late mechanisms of tumor progression control in the carcinogenesis pathway.

Conflict of Interests
The authors have no conflict of interests to declare.

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