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Adiponectin Is Inversely Associated With Tumour Grade in Colorectal Cancer Patients

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Abstract. *Background/Aim: Colorectal cancer is frequently associated with metabolic diseases. Adiponectin (APN) is an insulin-sensitizing adipokine circulating as low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) oligomers; the latter are the most bio-active oligomers. APN, through AdipoR1, AdipoR2 and T-cadherin receptors, regulates inflammation, and proliferation. Considering the anti-proliferative and anti-inflammatory properties of APN, we investigated the involvement of the "APN system" in colorectal cancer. Materials and Methods: A total of 44 colorectal cancer patients and 51 healthy controls were recruited. We analysed APN and HMW oligomers in sera, AdipoR1, AdipoR2 and T-cadherin expression in non-cancerous and cancerous colon tissues. Results: we found statistically lower levels of APN in patients compared to controls, with a specific decrease of HMW oligomers. Importantly, APN correlated to cancer grade. AdipoR1 was found overexpressed in cancerous compared to non-cancerous tissues while AdipoR2 and T-cadherin were down-regulated. Conclusion: The deregulated expression of the "APN system" in colorectal cancer with a specific correlation to tumor grade suggests APN as a promising biomarker in colorectal cancer.*

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Colorectal cancer is one of the most common tumours with high morbidity and mortality rates worldwide (1). Numerous studies have correlated colorectal cancer to obesity (1-3); in particular, abdominal adiposity, through its pro-inflammatory effects, as well as by oxidative stress, and metabolic pathways, has been indicated as predisposing factor to colon cancer (1-3). Adiponectin (APN) is a hormone abundantly produced by adipose tissue and secreted in the serum as oligomers of different molecular weight: low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) (2). Among the different oligomers, the HMW have the highest biological activity (2). APN is recognized to have multivalent beneficial biological functions in the regulation of energy homeostasis and insulin sensitivity (3, 4) as well as a key role in the inflammatory responses and proliferation processes (5). APN plays its pleotropic beneficial role *via* AdipoR1, AdipoR2 and T-cadherin receptors. AdipoR1 is predominantly expressed in striated muscle, while AdipoR2 is mainly expressed in the liver (6, 7). T-cadherin may also function as a third receptor for hexamer and HMW APN, responsible for the APN protective effects towards cardiovascular disorders (8). Furthermore, recent evidence suggests that T-cadherin is crucial for APN-mediated beneficial effects in the control of inflammation and proliferation (8, 9).

Recent studies demonstrated the key role of obesity in the development and progression of different cancers; in particular, the role of the metabolic adipose tissue perturbations due to chronic inflammation that represent a hormonal status promoting cell transformation, cancer development and directly influencing cancer progression, was highlighted (5, 9, 10).

In this context, different adipokines have been associated with colorectal cancer; in particular, epidemiological and *in*

vitro studies have evidenced the involvement of APN in this cancer (11, 12); in addition, the expression levels of APN receptors have been correlated to tumour growth, invasion and lymphogenic metastasis (13, 14). However, the data concerning APN serum levels in colorectal cancer patients are still contrasting (12, 14). In a previous *in vitro* study, we found that APN treatment negatively regulates cell survival and migration of both CaCo-2 and HCT116 human colorectal cell lines (15).

The aim of the present study was to investigate APN expression in the serum from 44 colorectal cancer patients to explore it as potential biomarker for tumour presence. In addition, we analyzed the APN oligomerization status to verify the presence of HMW, the most biologically relevant oligomers. Next, we compared the expression of AdipoR1, AdipoR2 and T-cadherin in 20 non-cancerous *vs*. cancerous colon tissues from patients.

Materials and Methods

Patients. In this cross-sectional study, 44 consecutive patients (32 males and 12 females, mean age=67.66±11.01, range=49-87 years) with diagnosis of colorectal cancer were enrolled from the Unit of Gastrointestinal Surgery, University of Campania "Luigi Vanvitelli". Exclusion criteria were: BMI >30, metabolic syndrome, type 1 and 2 diabetes, Inflammatory Bowel Disease (IBD), familial adenomatous polyposis (FAP), Lynch and Gardner syndromes, patients treated with preoperative chemotherapy and/or radiotherapy or with immunosuppressor drugs and subjects affected by acquired immunodeficiency. Serum from 51 volunteer normal subjects (31 males and 20 females, mean age=63.35±12.57, range=33-88 years) were recruited from the CEINGE staff as a control group. All subjects signed an informed consent form. The study was approved by the Ethics Committee of the Università della Campania "Luigi Vanvitelli" (Prot. 587/2018). All patients received radical resection (R_0), adequate lymphadenectomy and histological analysis in order to establish the tumour type and location, the tumour grade and stage of disease; for each patient, the "grade" of the tumour was documented and represented as follows: Grade 1 (G_1-well-differentiated tumour), Grade 2 (G_2-mild differentiated tumour) and Grade 3 (G_3-poorly differentiated tumour).

The expression of AdipoR1, AdipoR2 and T-cadherin receptors was investigated on tissues from the colon (healthy and tumor biopsies) from the first twenty consecutive patients.

Ethics statement. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Ethic Committee of the Università della Campania "Vanvitelli" (Prot. 587/2018).

Anthropometric and biochemical characteristics. Blood samples were collected after a 12-h overnight fasting period and centrifuged to collect serum. BMI was calculated as previously reported (16). For all participants, total cholesterol, triglycerides, glucose, aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transferase (GGT) levels were measured (Table I). The concentration of total APN in serum was measured by enzyme-linked immunosorbent assay (ELISA) method using an in house produced polyclonal antibody designed *vs*. a human APN amino acid region (H2N–ETTTQGPGVLLPLPKG–COOH). In detail, ELISA plates were coated with serum dilutions of (100 μl) in carbonate-bicarbonate buffer (0.1 mol/l, pH 9.6). A human recombinant adiponectin was used as the standard (Phoenix Pharmaceuticals, Burlingame, CA) as previously reported (16).

Western blot analysis of serum and tissues. Five micrograms of total serum proteins were treated as previously described (15). All samples were tested three times in duplicates. Incubation with APN antibodies was performed as previously described (15).

Colon tissues (healthy and tumour biopsies) were lysed and homogenized in RIPA buffer (Sigma-Aldrich, St. Louis, MO, USA). The lysate proteins were quantified by the Bradford method and 25 μg of proteins were dissolved in 1x Laemmli buffer and separated using 10% SDS-PAGE gel, as previously described (17). Incubation with AdipoR1, AdipoR2 (Santa Cruz Biotechnology, Dallas, TX, US), T-cadherin (Abcam, Cambridge, UK) and GAPDH primary antibodies (Sigma-Aldrich, St. Louis, MO, USA) was performed according to the manufacturer's instructions. The blots were developed by ECL (Amersham Biosciences, Piscataway, NJ, USA) and Kodak BioMax Light film and digitalized with a scanner (1,200 dpi) and analyzed by densitometry with the ImageJ software (http://rsbweb.nih.gov.ij/).

Gel filtration analysis. APN oligomeric distribution was analyzed by Gel Filtration Chromatography on a Superdex 200 10/300 GL column connected to a fast protein liquid chromatography system (Amersham Pharmacia Biotech, Uppsala, Sweden). A total of 1,875 μg total proteins were fractionated as previously described (16). The analysis was performed on 5 controls and 5 colorectal cancer patients. Fractions (250 μl) were collected and APN was quantified using ELISA and visualized by western blot analysis.

Statistical analysis. Continuous variables are given as mean±standard deviation. The Student's *t*-test and the nonparametric Mann-Whitney tests were used to determine differences between mean values for normally and, respectively, non-normally distributed variables. Categorical variables are reported as percentage and analyzed by either the Chi-square or the Fisher's exact test, where appropriate. A p-value <0.05 was considered to indicate statistically significant results. One-way analysis of variance (ANOVA) was used to compare APN levels in high- and low-grade and normal groups and Bonferroni's *t*-test for multiple comparisons. A multiple linear regression model was used to evaluate the relationship between APN levels with sex, BMI, cholesterol, triglycerides and APN levels as covariates.

Results

Surgical and baseline features. Tumour localization: in 10 patients, tumour was located in the right colon (22.72%), in 28 patients (63.63%) in the left colon, in 3 patients (6.81%) in the transverse colon and in 3 patients (6.81%) in the rectal tract. Of 44 patients, 10 patients (22.72%) underwent right hemicolectomy surgery, 26 left hemicolectomy, 2 anterior resection of sigmoid colon, 1 abdominal-perineal resection, 2 anterior resections of rectum and 3 transverse colectomies. Grade 1 (G_1) was documented in 15 patients (34.09%) while in 29 patients (65.90%) a Grade 3 (G_3) was recorded. No

Table I. *Comparison of anthropometric and biochemical features between controls and colorectal cancer patients.*

Parameters	Patients	Controls	*p*-Value
Gender (male)*	32 (72.7%)	31 (60.8%)	0.219
Age (years)**	67.66±11.01	63.35±12.57	0.067
BMI**	26.62±3.29	24.87±2.43	0.009
Total cholesterol (mg/dl)**	174.25±39	187.17±43.29	0.137
Triglycerides (mg/dl)**	106.95±35.47	108.86±43.94	0.820
Glycemia (mg/dl)**	94.16±32.77	93.71±22.32	0.937
AST (U/l)**	18.16±5.33	20.52±6.15	0.054
ALT (U/l)**	18.39±9.80	22.02±11.72	0.112
GGT (U/l)**	26.18±21.73	30.19±23.84	0.474
APN**	10.53±2.38	13.38±3.37	<0.001

Data are expressed as mean±SD. *Pearson's Chi-Square Test. **Student's *t*-test and Mann-Whitney test.

Table II. *APN levels are independent from anthropometric and biochemical parameters in GC patients.*

Parameters	Beta	*p*-Value
Gender	–0.084	0.605
BMI	0.067	0.686
Total cholesterol	–0.131	0.474
Triglycerides	–0.041	0.805
Glycemia	-0.051	0.777

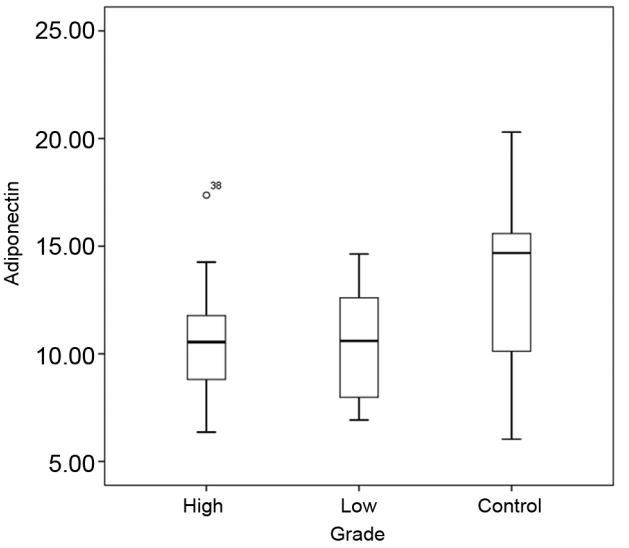

Figure 1. *APN levels correlate to grade of disease. APN levels in colorectal cancer patients compared to healthy controls. Colorectal cancer patients were divided in two subgroups according to grade: G1 (well-differentiated tumour), G3 (poorly-differentiated tumour).*

patient presented tumour grade 2 (G_2). The anthropometric and biochemical characteristics of colorectal cancer patients and sex and age-matched control group are reported in Table I. The two groups statistically differ for BMI ($p<0.003$).

APN serum levels correlate to colorectal cancer grade. APN levels are statistically lower in serum from patients affected by colorectal cancer than in controls (10.53 μg/ml ±2.38 *vs*. 13.38 μg/ml±3.37, $p<0.01$). The multiple linear regression analysis, after correction for confounding factors (sex, BMI, total cholesterol, triglycerides and glucose) confirmed a significant decrease of APN levels in patients affected by colorectal cancer (Table II). Interestingly, APN levels are correlated to the grade of the colorectal cancer disease (Figure 1). Grade 3 (G3 -poorly differentiated tumour) patients have lower levels of APN with respect to Grade 1 (G1-well-differentiated tumour) patients as well as healthy control subjects suggesting a functional regulation of APN strictly dependent on disease severity.

Oligomeric distribution of APN. APN oligomeric distribution in colorectal cancer patients was characterized by western blot analysis (Figure 2) as well as by fast protein liquid chromatography (FPLC) (Figure 2). Both analyses confirmed that colorectal cancer patients had reduced levels of total APN and evidenced that all three APN oligomers are decreased. In particular, the HMW oligomers, the most biologically relevant oligomer ($p<0.05$), are also reduced.

Expression tissue analysis of AdipoR1, AdipoR2 and T cadherin. We investigated the expression of APN receptors in 20 non-cancerous and cancerous colorectal tissues. We found that APN receptors are differentially expressed in non-cancerous tissues compared to cancerous tissues (Figure 3). In particular, AdipoR1 expression is increased in cancerous tissues compared to non-cancerous tissues, while AdipoR2 and T-cadherin are reduced in cancerous tissues compared to non-cancerous tissues ($p<0.05$).

Discussion

In this study, we performed an integrated analysis on "APN system" in patients affected by colorectal cancer. The analyzed patients have significantly higher BMI, triglycerides, glucose, and a significantly decreased expression of total APN associated with lower levels of HMW oligomers. Interestingly, statistical analysis indicated that reduced APN levels are independent from sex, BMI, triglycerides, glucose and total cholesterol but are correlated to disease's severity. In addition, we demonstrated a modulation of the expression of AdipoR1, AdipoR2 and T-cadherin receptors in non-cancerous compared to cancerous tissues. Altogether, our results indicate an involvement of the "APN system" in colorectal cancer.

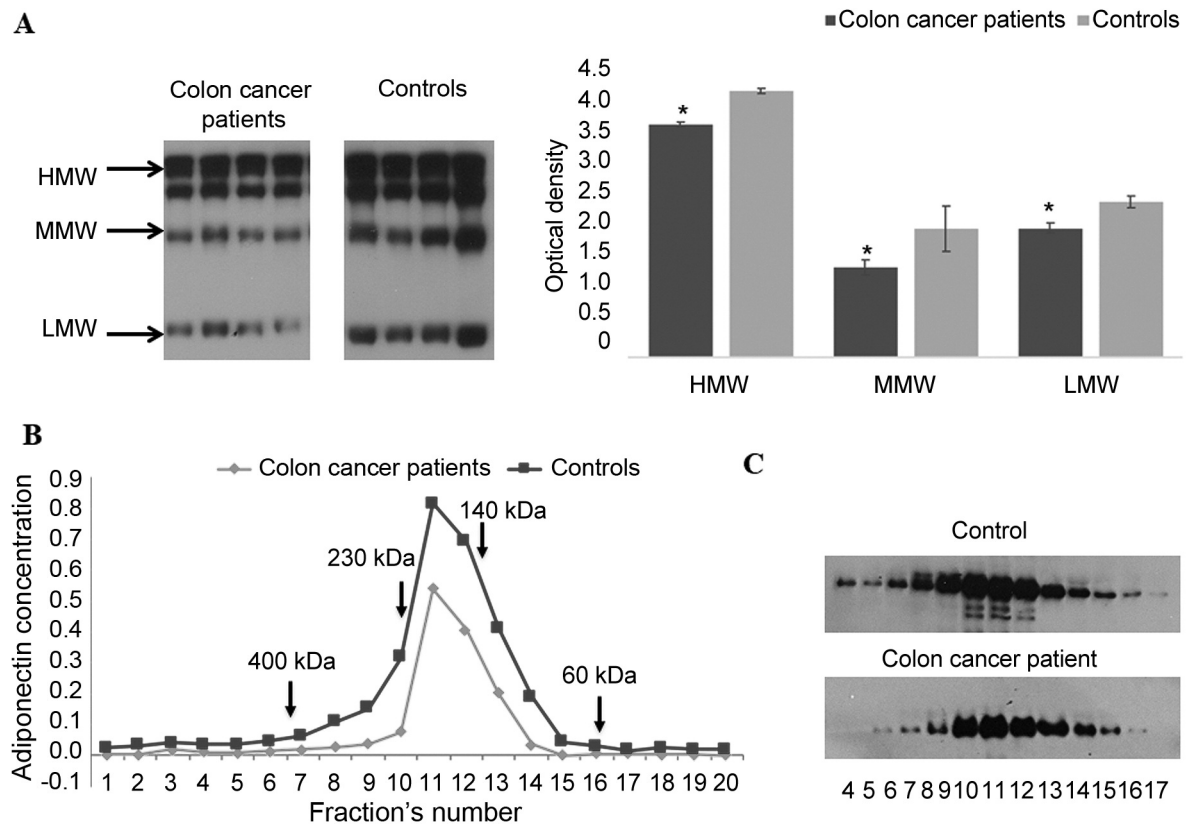

Figure 2. *APN HMW oligomers, analyzed by western blotting and FPLC analysis, are reduced in serum from colorectal cancer patients compared to healthy controls. (A) Representative WB image of APN different oligomers (HMW, MMW, LMW) from four controls and four colorectal cancer patients. Graphical representation of pixel quantization of APN oligomers analyzed in 51 controls and 44 colorectal cancer patients. (B) Each fraction's aliquot obtained from FPLC analysis was subjected to ELISA. The values are reported as mean of absorbance±S.D. (C) One representative image of each fraction subjected to WB analysis. For other details see materials and methods. *p<0.05.*

Colorectal cancer, one of the most frequent cancers worldwide, has been previously associated with obesity and metabolic diseases (6, 18). Recently, the aberrant activities of adipose tissue (such as the dysregulated secretion of adipokines, angiogenesis, hypoxia) that occur in metabolic diseases have been identified as a hormonal status favourable to cell transformation and cancer development; this hormonal aberrant context may directly influence cancer progression (5, 9, 10). The dysregulated secretion of adipokines also includes APN that has a key role in different cellular processes, such as inflammation and cell growth (19). In colorectal cancer, the important role of APN and its receptors (AdipoR1, AdipoR2 and T-cadherin) appears from epidemiological and *in vitro* studies (11, 12); in particular, the expression of APN receptors has been associated with tumour growth, invasion and lymphogenic metastasis (13, 14). However, data on APN serum levels in colorectal cancer patients are complex and still controversial. Indeed, Otake *et al*., (20) reported that low APN levels represent an important risk factor for colorectal adenoma. Similarly, Xu *et al*., demonstrated that patients with colorectal cancer and adenoma have significantly lower APN values compared to healthy controls (21). Finally, Ferroni *et al*., (22) found low APN serum concentrations to be a complementary tool in the prediction of risk for colorectal cancer recurrence. On the contrary, Lukanova *et al*., (23) did not identify any relationship between plasma APN levels and colorectal cancer; Wei *et al*., (24) and Yamaji *et al*. (25) found a direct association of total APN with obesity and an inverse association with colorectal cancer. Another case control study reported that APN concentration is higher in colorectal cancer patients compared to IBD and healthy control groups (26). In the present study, we found a statistically significant decrease of total serum APN and for the first time we also found a decrease of all three oligomeric forms (LMW, MMW, HMW). The lower levels of HMW, being the oligomers with the highest biological activity of APN (2), confirm the specific a specific involvement of this adipokine in colorectal pathology.

Regarding APN receptors, our study demonstrated that the expression of AdipoR1, AdipoR2 and T-cadherin is differently modulated between non-cancerous and cancerous

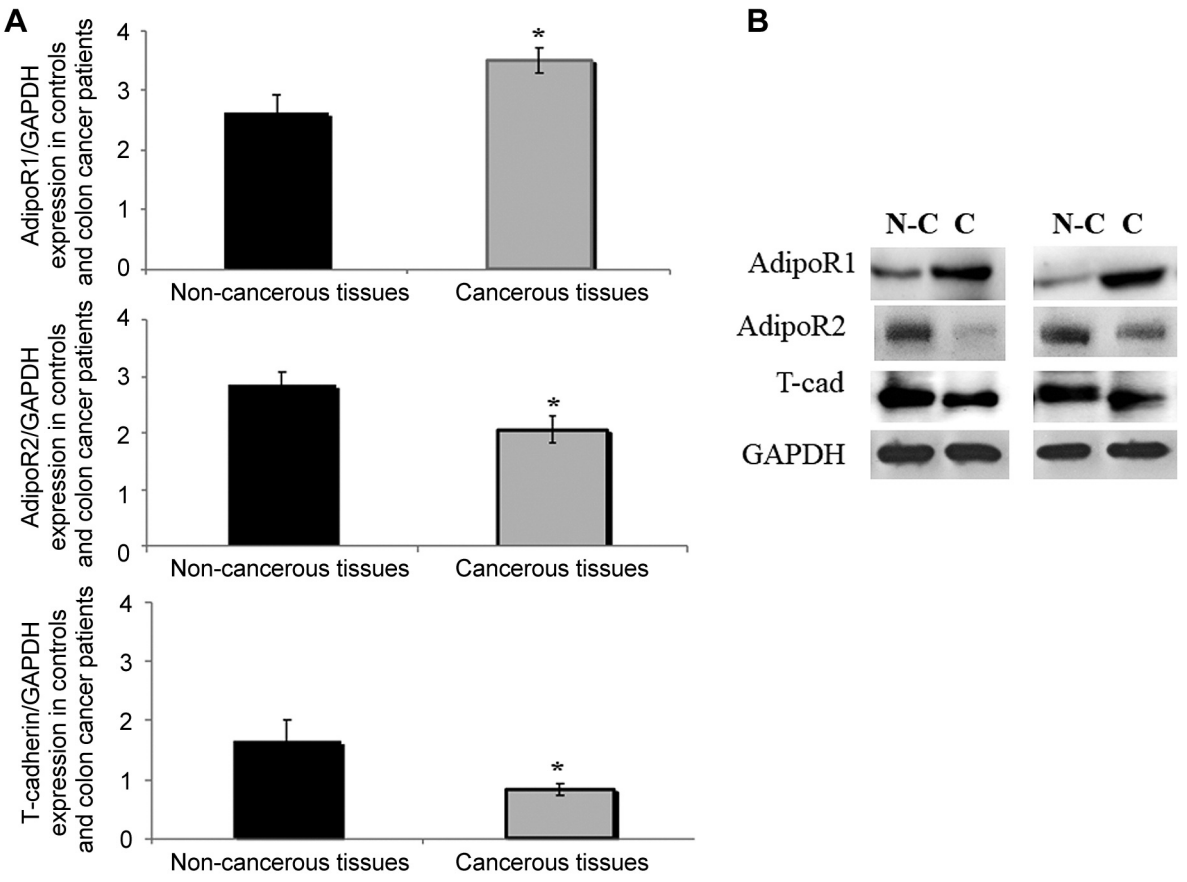

Figure 3. *AdipoR1, AdipoR2 and T-cadherin expression is differently modulated in cancer tissues compared to non-cancer tissues. (A) Graphical representation of pixel quantization of AdipoR1, AdipoR2 and T-cadherin expression analyzed in 20 non-cancer tissues and 20 cancer tissues through WB analysis. (B) Representative western blotting image of AdipoR1, AdipoR2, T-cadherin and GAPDH in non-cancer tissues compared to cancers tissues. *p<0.05.*

tissues; indeed, AdipoR1 expression was higher while the T-cadherin and AdipoR2 expression decreased in tumour cancer compared to non-cancerous tissues. Differently to our data, Yoneda *et al*., showed that Adipo-R1 and Adipo-R2 were not differently expressed in normal colon epithelium and colorectal cancer tissues (27). On the contrary, previous studies have described T-cadherin as an anti-tumor gene, as its expression is suppressed in several types of cancer (28). T-cadherin has been reported to inhibit tumor cell proliferation and invasion, whereas reduced T-cadherin was associated with a poor cancer prognosis (29) and colorectal carcinogenesis (8). Furthermore, Toyooka *et al*., (30) showed that colorectal cancers and adenomas are frequently characterized by the hypermethylation of the T-cadherin gene promoter region. Also, Hibi *et al*., (31) found that almost all (83%) of poorly differentiated colorectal cancers have a higher T-cadherin methylation. Accordingly, our results suggest that down-regulation of T-cadherin expression in our cancer tissues plays a functional role in colorectal cancer trough mechanisms also involving APN and its most biologically active HMW oligomers.

Several studies have shown the protective role of APN in obesity-associated diseases and cancer regression. The findings of our study confirmed that APN is also involved in colorectal cancer disease. Indeed, the analysis of APN serum levels showed that the expression of this adipokine is decreased and characterized by a lower concentration of HMW, the oligomers with the highest biological activity. In addition, total APN levels showed an association with disease severity. Furthermore, we found a modulation of the expression of APN receptors in non-cancerous and cancerous colon tissues. Validation in larger studies will confirm our data. Further studies are needed to better understand the involvement of APN and its potential use in the pathophysiology of colorectal cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

AD and LF conceived the study. AD, SN and EN wrote the manuscript. RP, EN and MLM performed the experiments. GS performed the statistical analysis. RDA, LDM recruited the patients and performed the histological analysis. LF and RDA performed the surgical procedures. The final version of the manuscript was approved by all the Authors.

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