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SIRT1 gene polymorphisms and its protein level in colorectal cancer

Olfat Gamil Shaker[a], Miriam Safwat Wadie[a,*], Reham Maher Mohamed Ali[a], Ayman Yosry[b]

[a] Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Cairo University, Cairo 11562, Egypt
[b] Tropical Medicine Department, Faculty of Medicine, Cairo University, Cairo 11562, Egypt

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ABSTRACT

Colorectal cancer (CRC) is a major cause of mortality and morbidity, and accounts for over 9% of cancer incidence worldwide. Nuclear localized silent information regulator 2 homolog 1 (SIRT1) gene exerts its effects via modulation of histone and non-histone targets. SIRT1 gene functions in the cell via histone deacetylase (HDAC) and/or adenosine diphosphate ribosyl transferase (ADPRT) enzymatic activity. The aim of this work is to study the relationship between SIRT1 polymorphism and its protein level in colorectal cancer patients in comparison to control cases. This study includes two group, thirty healthy subjects (control group) and one hundred CRC patients. SIRT-1 serum level was measured in both the groups by ELISA and gene polymorphisms of rs12778366, rs375891 and rs3740051were detected by real time PCR. For CRC patients clinical data was collected including tumor size, tumor grade, tumor site, obesity. CRC patients showed a significant increase in the mean level of serum SIRT-1 compared to control group ($P < 0.001$). Mean serum level of SIRT-1 showed a significant increase in patients with tumor size ≥ 5 cm compared to the size < 5 cm ($P < 0.05$). In CRC patients, the percentage of T allele of rs12778366 was significantly lower than controls, CC genotype and C allele C of rs375891 were significantly higher than control group. In CRC patients, the CC genotype of rs12778366, was 75% in the rectosigmoid colon and 25% in cecum & ascending colon. According to tumor size, the percentage of CC genotype was 87.5% in tumor size ≥ 5 cm.

Conclusion: Serum level of SIRT-1 and T allele, C allele of rs12778366 and rs375891 respectively can be used as diagnostic markers for CRC patients.

1. Introduction

Colorectal cancer (CRC) is a major cause of mortality and morbidity, and accounts for over 9% of cancer incidence worldwide. The prevalence of colon and rectum cancer is rapidly rising in areas that are historically known to be of low risk and the cause of this emerging trend seems to be due to a combination of factors that affect lifestyle and environment (Jemal et al., 2011). Colorectal cancer rates are changing and following an unequal population distribution and burden around the world (Henry et al., 2009).

Silent information regulator 2 (SIR2) is an antiaging gene that was originally discovered in budding yeast which encodes a protein with NAD + dependent histone deacetylase activity (Fessel et al., 2011). SIRT1 is one of seven homologs of SIR2 in mammals (Imai and Guarente, 2010) which are involved in cell energy metabolism, proliferation, senescence, multiple inflammatory processes, neuroprotection, tumorigenesis amongst others (Michan and Sinclair, 2007).

There are many controversies on the role of SIRT1 in tumors (Song and Surh, 2012). The controversy over whether SIRT1 serves as a tumor promoter or a tumor suppressor has not been completely resolved and the discussion will likely continue (Song and Surh, 2012).

The aim of this study is to investigate SIRT1 expression in CRC patients in comparison to a control group and to detect if there is a relation between its expression and the clinicopathological data of CRC patients. The study also aimed at studying SIRT1 polymorphisms (rs12778366, rs375891, rs3740051) in CRC patients and the control group.

2. Material and methods

2.1. Study subjects

This study included 130 Egyptian individuals classified into two groups:

Group (1): included one hundred CRC patients (68 male and 32 female) average age 50.4 ± 12.2 (mean ± SD), range 27–73 years.

Abbreviations: SIR2, Silent information regulator 2; CRC, Colorectal cancer; SIRT1, Silent information regulator 2 homolog 1

* Corresponding author.
E-mail address: miriam.safwat@kasralainy.edu.eg (M.S. Wadie).

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All patients were enrolled from the tropical medicine department, Kasr Al-Aini Hospital, Cairo University from January 2015 to July 2015. The CRC patients had different sites of cancer including ascending colon, transverse colon, hepatic and splenic flexures and rectosigmoid colon. All CRC patients were newly diagnosed with positive colonoscopy and confirmed by pathology. Colonoscopy was recommended in cases with a positive fecal occult blood test, hemorrhoids, abdominal pain of unknown origin, or macroscopic bleeding. None of the patients received chemo- and/or radiotherapy before collection of blood samples. Patients with history of secondary or recurrent tumors were excluded from the study.

Group (2): included thirty healthy subjects (control group) (16 male and 14 female). Controls had negative colonoscopy results for malignancy or IBD and had no history of familial adenomatous polyposis or hereditary non-polyposis CRC.

An informed consent was obtained from all subjects enrolled in this study. The study protocol was approved by the ethics committee of the Faculty of Medicine, Cairo University, and conformed to the ethical guidelines of the 1975 Helsinki Declaration.

2.2. Blood sampling

Venous blood samples (~5 ml) were collected by trained laboratory technicians and a complete blood analysis was performed. Blood was divided into 2 tubes under aseptic conditions as follows:

A portion of blood (3 ml) was allowed to clot and then centrifuged at 3500 × *g* for 5 min to separate the serum used for routine laboratory investigations: renal functions, liver functions, and SIRT-1 level measurement.

A second portion of blood (2 ml) was collected in EDTA Vacutainer tubes and stored at − 80 °C until DNA extraction.

2.3. DNA extraction

DNA was extracted from whole blood using Qia-amplification DNA extraction kit (Qiagen, USA).

2.4. Genotyping of SNPs in SIRT-1 (rs12778366, rs3758391, rs3740051)

Genotyping was performed using real-time polymerase chain reaction with TaqMan allelic discrimination assay (Applied Biosystems, USA).

The 3 studied SNPs were located in the 5′ flanking region of the SIRT1 gene. We used Tagger software (http://www.broadinstitute.org/mpg/tagger/) to select tag SNPs in the SIRT1 region plus 0.5 Kb downstream, and 30 Kb upstream (NCBI Build 35/UCSC hg17), the minor allele frequency > 5% in Caucasian population and r2 > 1 as criteria.

2.4.1. PCR amplification protocol

A predesigned primer/probe sets for the 3 genotypes were used (Applied Biosystems, USA). Probes were synthesized with reporter dye FAM or VIC covalently linked at the 5/and a quencher dye MGB linked to the 3/end of the probe. The *rs12778366* (*C_1340370_10*), *rs3758391* (*C_3003909_10*) *and rs3740051* (*C_27471644_10*) *were supplied by* (Applied Biosystems, USA). DNA amplification was carried out in a 25 μl total volume containing:12.5 μl Taqman master mix.,1.25 primer/probe, 1 μl DNA (100 μg), 10.25 H_2O. Real-time PCR was performed using a Rotor gene Q Real Time PCR System (Qiagen, Valencia, CA, USA) with the following conditions: after a denaturation time of 10 min at 95 °C, 45 cycles at 92 °C for 15 s then 60 °C for 90 s for annealing and extension were carried out and fluorescence was measured at the end of every cycle and at the endpoint.

2.5. Estimation of serum SIRT-1 by enzyme linked immunosorbent assay

SIRT1 was quantitated in serum by using an ELISA kit provided by Sun Red, Shanghai, China. The kit is a double-antibody sandwich enzyme-linked immunosorbent assay. The serum was added to a precoated well with specific SIRT1 monoclonal antibody. SIRT1 antibody labeled with biotin was added after incubation, and then Streptavidin-HRP was added to form an immune complex. Washing was done to remove the uncombined enzyme. Chromogen Solutions A, B, were added to give the blue color. The reaction was stopped by the effect of a stop solution. The color in the wells and the concentration of the human Substance SIRT1 of sample were positively correlated.

2.6. Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science) version 22. Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests (Chan, 2003a).

For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is < 5 (Chan, 2003b). ROC curve was constructed with the area under curve analysis performed to detect the best cutoff value of SIRT1 for detection of CRSC. P-values < 0.05 were considered as statistically significant.

3. Results

The demographic data of the studied groups are presented in Table 1. There were no significant differences between the 2 groups as regards to age, sex and obesity, (P > 0.05).

The clinical data of CRC patients is summarized in Table 2. The site of the tumor was rectosigmoid in 66%, transverse colon and flexures was 21% and cecum and ascending colon was 13%. The size of tumor was < 5 cm in 41% and equal or > 5 cm in 59%. As regards to tumor grade, high grade in 62% and low grade in 38%.

SIRT1 protein expression in both groups is shown in Table 3. CRC patients showed a highly significant increase in the mean level of serum SIRT-1 as compared to the control group (737.30 versus 443.80, P < 0.001) (Fig. 1). Mean level of serum SIRT-1 showed a highly significant increase in patients with tumor size ≥5 compared to the size < 5 cm. Regarding the site, there was no significant difference between the different sites. As regards to the grade of adenocarcinoma (high and low) or the obesity in CRC patients, both showed non-significant differences (Table 4).

In CRC patients, percentage of SIRT-1 (rs12778366) T allele (Table 5 and Fig. 2), SIRT-1 (rs375891) CC genotype and allele C was significantly higher than control group (Table 6 and Fig. 3).

We studied SIRT1 gene polymorphism (rs12778366), according to tumor site. In the rectosigmoid colon the genotypes (CC, CT, TT) were 75%, 63.6%, 65.4% respectively. In the transverse colon & flexures, it was 0%, 0% and 25.9% respectively. Meanwhile, it was 25%, 36.4%

Table 1
Demographic data of the studied groups.

		CRC patients (100) Group (1)	Control (30) Group (2)	P value
Age (years)		50.4 ± 12.2	46.9 ± 9.6	0.184
Sex (%)	Male	68%	53.3%	0.141
	Female	32%	46.7%	
Obesity (%)	Yes	49%	46.7%	0.823
	No	51%	53.3%	

Age is expressed as mean ± SD, sex and obesity in the form of percentage.

Table 2
Clinical data of CRC patients.

		Count	%
Site of tumor	Rectosigmoid	66	66%
	Transverse colon and flexures	21	21%
	Cecum and ascending colon	13	13%
Size of tumor	< 5 cm	41	41%
	≥ 5 cm	59	59%
Adenocarcinoma grading	High grade	62	62%
	Low grade	38	38%

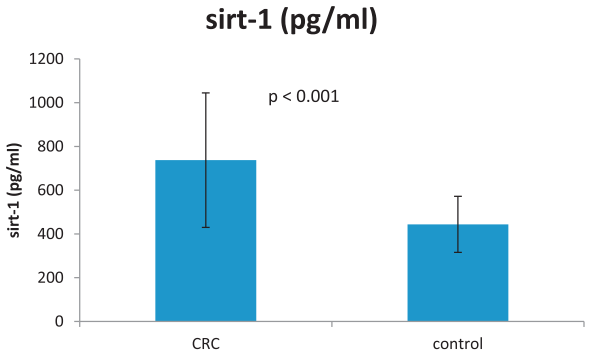

Fig. 1. SIRT1 expression in CRC patients and control group.

Table 3
SIRT1 protein expression in both groups.

	CRC patients	Control	P value
SIRT1 (pg/ml)	737.30 ± 307.34	443.80 ± 128.27	0.001

Table 4
Statistical analysis of SIRT1 expression in CRC patients versus clinical data.

		SIRT-1 (pg/ml) Mean	SD	P value
Site of tumor	Rectosigmoid	741.53	317.62	0.912
	Transverse colon & flexures	717.67	254.94	
	Cecum & ascending colon	747.54	351.60	
Size of tumor	< 5 cm	678.68	281.49	0.034*
	≥ 5 cm	778.03	320.10	
Adenocarcinoma grade	High grade	751.26	304.66	0.325
	Low grade	714.53	314.41	
Obesity	Yes	787.45	325.61	0.121
	No	689.12	283.57	

* The tumor ≥ 5 cm has statistical significant difference increase in the mean level of SIRT-1 compared to the size < 5 cm P value = 0.034.

and 8.6% in the cecum & ascending colon respectively. According to tumor size, the percentage of CC, CT, TT was 12.5%, 81.8%, 38.3% respectively with tumor size < 5 cm. In tumor size ≥ 5 cm, it was

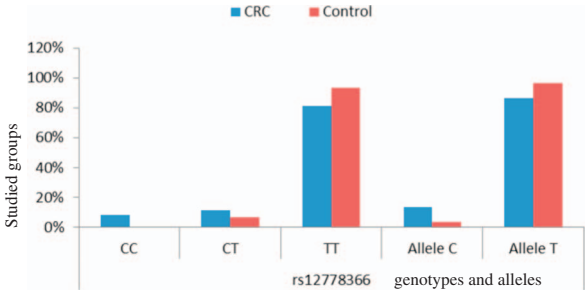

Fig. 2. SIRT-1 (rs12778366) genotypes and alleles in the two studied groups.

87.5%, 18.2%, 61.7% respectively (Table 7).

In CRC patients, there was significant statistical difference between SIRT-1 (rs3740051) genotypes as regards to tumor size and site. According to tumor site, the percentage of AA, AG, GG in the rectosigmoid colon was 69.7%, 64.7%, 28.6% while in the transverse colon and flexures was 18.4%, 35.3%, 14.3% and in cecum & ascending colon was 11.8%, 0%, 57.1% respectively. According to tumor size, the percentage of AA, AG, GG was 47.4%, 29.4%, 0% in tumors < 5 cm. Tumors ≥ 5 cm the percentage was 52.6%, 70.6%, 100% (Table 8).

4. Discussion

Colorectal cancer occurs in the colorectal mucosa and colonic glands and is one of the most common types of malignant tumors of the digestive system (Siegel et al., 2014).It is a major cause of morbidity and mortality throughout the world and is the third most common cancer worldwide (Bazensky et al., 2007).Staging of disease at diagnosis is a critical factor affecting survival. When discovered early, CRC is highly treatable, with a relative five-year survival rate of 90% for localized CRC (Courtney et al., 2013).

Because there is potential links between SIRT1, calorie restriction and cellular energy balance (Bishop and Guarente, 2007), we examined the relations between SIRT1 expression and obesity. We studied obesity in CRC patients but gave us non-significant results (P > 0.05). Our finding was in agreement with (Donohoe et al., 2011) who found that there was no significant relationship between obesity & occurrence of CRC. Age & sex also show no significant difference with CRC.

SIRT1, the human homolog of Sir2, is a member of sirtuins family. SIRT1 is a NAD1 dependent class III deacetylase (HDAC) which can deacetylate both histone and non- histone proteins (Cohen et al., 2004). The importance of histone deacetylases in cancer development has become increasingly apparent. Many non-histone protein targets of histone deacetylases have been identified as tumor suppressors or promoters, and aberrant expression and regulation of histone deacetylases therefore has been shown to have either oncogenic or protective consequences (Singh et al., 2010).

SIRT1 impacts a diverse variety of biological activities, with > 50 non histone protein targets currently identified. Some of the more worthy targets relevant to carcinogenesis are those that function in the DNA damage response, autophagy, cellular metabolism, and cell survival under stress (Yuan et al., 2013).

Table 5
SIRT-1 (rs12778366) genotypes and alleles in the two studied groups.

		CRC (100) Count	%	Control (30) Count	%	P value	OR (95% CI)
rs12778366	CC	8	8.0%	0	0.0%	0.197	–
	CT	11	11.0%	2	6.7%	0.731	1.730 (0.362–8.279)
	TT	81	81.0%	28	93.3%	0.157	0.305 (0.067–1.391)
	Allele C	27	13.5%	2	3.3%	0.028*	4.526(1.44–19.621)
	Allele T	173	86.5%	58	96.7%		

* Allele T was 96.7%, with significant difference between patients and controls (P < 0.05).

Table 6
SIRT-1 (rs375891) genotypes and alleles in the two studied groups.

		CRC (100) Count	%	Control (30) Count	%	P value	OR (95% CI)
rs375891	CC	47	47.0%	4	13.3%	0.001*	5.764 (1.874–17.729)
	CT	39	39.0%	21	70.0%	0.003*	0.274 (0.114–0.659)
	TT	14	14.0%	5	16.7%	0.770	0.814 (0.267–2.480)
	Allele C	133	66.5%	29	48.3%	0.011	2.122 (1.182–3.810)
	Allele T	67	33.5%	31	51.7%		

* SIRT-1 polymorphism (rs375891) genotypes and alleles. The percentage of CC, CT, TT were 47%, 39%, 14% respectively, allele C was 66.5% in CRC patients. Meanwhile, the percentage of CC, CT, TT were 13.3%, 70%, 16.7% respectively & allele C was 48.3% in controls. OR for CC, CT, TT were 5.764, 0.274, 0.814 respectively and was 2.122 for alleles. There is significant difference in genotypes CC & CT ($P < 0.05$ each).

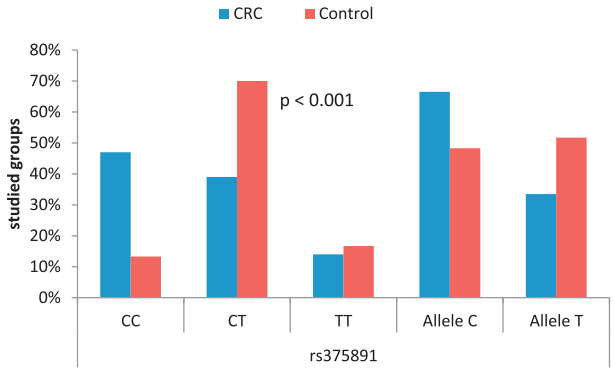

Fig. 3. SIRT-1 (rs375891) genotypes and alleles in the two groups.

In the present study, SIRT1 protein level was measured by ELISA in CRC group and compared to controls and there was a significant difference between them ($P < 0.05$).This is the first report of SIRT1 measurement in serum of Egyptian CRC patients and our results mirror in part those of Risk et al. (2016) who found that serum levels of SIRT1 in breast cancer patients was significantly higher than controls ($P < 0.001$).

Our results are in agreement with Yu et al., 2016 who collected specimens from 40 patients undergoing surgical resection for the treatment of colorectal cancer between March 2010 and October 2012 at the Affiliated Xinhua Hospital of Dalian University. They measured the expression of SIRT1 and found that SIRT1 was highly expressed in the colorectal cancer samples in comparison to adjacent normal control mucosa tissue with $P < 0.05$.Also our results were in line with Chen et al. (2014) and Zhang et al. (2015) who collected specimens from patients and adjacent normal mucosa tissues as controls. They found that SIRT1 was highly expressed in CRC patients ($P < 0.05$).

Also in agreement with the present study is Jung et al. (2013) who studied immunohistochemical SIRT1 expression, DBC1, β-catenin, survivin, and p53 in human colorectal cancer and their relationships with clinicopathologic factors and prognostic significance in 349 CRC patients. They found that SIRT1 expression is observed in 235 (67%). All of the sampled normal mucosa showed weak SIRT1 expression with nuclear staining.

At the same time Kikuchi et al. (2013) studied the expressions of SIRT1 and DBC1 by immunohistochemical staining and western blot analysis from 114 patients and they found that SIRT1 expression was high in CRC patients. Their results coincided with ours.

There is a significant increase in the SIRT1 level in serum in cases of CRC with tumor size ≥ 5 cm. These results contradict that of Risk et al. (2016) who studied the significant difference in SIRT1 level in breast cancer & size of tumor, but found no statistical difference.

In the present study we found no significant relation between obesity & SIRT1 level ($P > 0.05$). Also there was no significant relation between SIRT1 expression and site of tumor or adenocarcinoma grade ($P > 0.05$). These results contradict Nosho et al. (2009) results, who found that SIRT1 overexpression was significantly associated with a high tumor grade ($P < 0.05$).

In agreement with our study, Chen et al. (2014) and Kikuchi et al. (2013) suggested that SIRT1 had no significant correlation to clinicopathological features such as age, gender, location and T-category. Meanwhile Chen et al. (2014) found that SIRT1 expression was significantly correlated with the number of cancer sites ($P = 0.03$), metastases ($P = 0.02$) and metastatic sites ($P = 0.02$). By using the Kaplan-Meier analysis, they found that strong SIRT1 expression of tumor tissue had an obvious association with poor prognosis in CRC patients .

ROC curve analysis for SIRT1 expression shows that AUC (area under the curve) was 0.825 and the best cut off value was 523 pg/ml with 76% sensitivity and 73.3% specificity. No previous results were found to compare with ours as this is the first time to put a cutoff value of SIRT1.

Table 7
SIRT-1 (rs12778366) genotypes and alleles & relation with tumor site, size, grade & obesity.

		rs12778366 CC Count	%	CT Count	%	TT Count	%	P value
Site	Rectosigmoid	6	75.0%	7	63.6%	53	65.4%	0.014*
	transverse & flexures	0	0.0%	0	0.0%	21	25.9%	
	Cecum & ascending	2	25.0%	4	36.4%	7	8.6%	
Size	< 5 cm	1	12.5%	9	81.8%	31	38.3%	0.004*
	> 5 cm	7	87.5%	2	18.2%	50	61.7%	
Grade	Low grade	2	25.0%	5	45.5%	31	38.3%	0.685
	High grade	6	75.0%	6	54.5%	50	61.7%	
Obesity	Yes	6	75.0%	5	45.5%	38	46.9%	0.361
	No	2	25.0%	6	54.5%	43	53.1%	

* The percentage of CC, CT, TT according to tumor site, in rectosigmoid the genotypes (CC, CT, TT) were 75%, 63.6%, 65.4% respectively. In transverse & flexures, it was 0%, 0% and 25.9%. Meanwhile, it was 25%, 36.4% and 8.6% in cecum & ascending colon. There was significant statistical difference between these genotypes and site of tumor $P = 0.014$. According to tumor size, the percentage of CC, CT, TT was 12.5%, 81.8%, 38.3% respectively with tumor size < 5 cm. In tumor size ≥ 5 cm, it was 87.5%, 18.2%, 61.7% respectively with $P = 0.004$.

Table 8
SIRT-1 (rs3740051) genotypes and alleles in relation to the clinical data of CRC patient.

		rs3740051 AA Count	%	AG Count	%	GG Count	%	P value
Site	Rectosigmoid	53	69.7%	11	64.7%	2	28.6%	0.008*
	Transverse & flexures	14	18.4%	6	35.3%	1	14.3%	
	Cecum & ascending	9	11.8%	0	0.0%	4	57.1%	
Size	< 5	36	47.4%	5	29.4%	0	0.0%	0.027*
	> 5	40	52.6%	12	70.6%	7	100.0%	
Grade	Low grade	31	40.8%	4	23.5%	3	42.9%	0.414
	High grade	45	59.2%	13	76.5%	4	57.1%	
Obesity	Yes	39	51.3%	8	47.1%	2	28.6%	0.562
	No	37	48.7%	9	52.9%	5	71.4%	

* SIRT-1 polymorphism (rs3740051) genotypes and alleles in relation to clinical data of CRC patients. The percentages of AA, AG, GG in rectosigmoid were 69.7%, 64.7%, 28.6% while in transverse colon and flexures were 18.4%, 35.3%, 14.3% and in cecum & ascending colon were 11.8%, 0%, 57.1%. There was significant statistical difference between these genotypes (P = 0.008). According to tumor size, the percentage of AA, AG, GG were 47.4%, 29.4%, 0% in size < 5. When the size was ≥ 5 the percentages were 52.6%, 70.6%, 100% respectively with (P = 0.027).

Lee et al. (2015) revealed a significant association between high SIRT1 expression and poor outcome in CRC patients. They also investigated the effect and molecular mechanism of the antipsychotic drug chlorpromazine (CPZ) and identified its potential for treating colorectal cancer (CRC) inhibiting sirtuin 1. They also found that CPZ induced the degradation of SIRT1 protein participating downstream of JNK, and JNK suppression abrogated CPZ-mediated SIRT1 downregulation. These data suggest that SIRT1 is an attractive therapeutic target for CRC and that CPZ is a potential repositioned drug for treating CRC.

To the best of our knowledge, our study is the first to study SIRT1 polymorphism (rs3758391, rs3740051, rs12778366) genotypes in CRC patients.

SIRT-1 (rs12778366) TT genotype was the most common in both CRC patients and control 81%, 93.3% respectively and T allele was the most common in CRC patients & control 86.5%, 96.7%. It showed a significant relation with the site & size of tumor $P < 0.05$, but there was no significant relation with obesity or the grade of tumor ($P > 0.05$).

SIRT-1 (rs375891) CC genotype was common in CRC patients and showed a very high significance (P = 0.001) while CT genotype was common in the control group ($P < 0.01$). C allele was common in CRC patients & T was common in the control group ($P < 0.05$). There was no significance correlation with the clinicopathological data of the patients. SIRT-1 (rs3740051) AA genotype was common in CRC patients and controls 76% & 80% respectively. A allele was the common but didn't show significance. But it showed significance with the site and size of tumor.

It is recommended to study SIRT1 expression and SIRT1 polymorphism (rs12778366, rs375891, rs3740051) on larger population. SIRT1 gene expression can be used as marker for CRC prognosis.

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